Endoscopic Therapy for Major Peptic Ulcer Haemorrhage

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Contents

Declaration

I declare that all the work contained in this thesis has been performed by myself unless otherwise stated herein.

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Ethical Permission

The trial which forms the basis of this thesis was given ethical approval by the Local Research Ethics Committee of each of the centres which enrolled patients. No individual was entered into the trial until the respective Ethics Committee had approved the trial.

Written consent was obtained from each patient, except in rare cases where the patient was too unwell or was mentally incapable to give informed consent. In these cases assent was obtained from the next of kin.

The trial was conducted in accordance with the requirements of Good Clinical Practice and complied with the Declaration of Helsinki.

The patients' general practitioner was informed by letter of the patients' participation in the study.

Local Ethics

Aberdeen	Grampian Research Ethics Committee.	Ref: 96/0345
Dundee	Tayside Committee on Medical Research Ethics.	Ref: 231/96
Edinburgh	Lothian Research Ethics Committee.	Ref: 1702/96/4/131
Glasgow	West Glasgow Ethics Committee.	Ref: AHT/NS/0023

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Abstract

Peptic ulcer bleeding is a major clinical emergency. Over the last 10 years therapeutic endoscopy has been routinely used in selected patients in an attempt to stop active bleeding and prevent re-bleeding. Trials have shown that endoscopic therapy reduces re-bleeding, the need for urgent surgery and mortality in patients with major bleeding from peptic ulcer. Only patients with active bleeding, non-bleeding visible vessels or tightly adherent blood clot require therapy; the remainder are at low-risk of further haemorrhage and are treated conservatively. The most commonly used endoscopic therapies are adrenaline injection and application of the heater probe, although thrombin injection has theoretical advantages over adrenaline and there is trial evidence to support its use. Combinations of injection and thermal treatments may confer additional benefit, but definitive evidence for this approach is lacking. This thesis is based on a randomised, placebo controlled trial comparing heater probe plus thrombin injection with heater probe plus placebo injection for the treatment of high-risk patients with peptic ulcer bleeding.

Two hundred and fifty six patients were randomised. There were nine protocol violations, and these were excluded from the analysis. One hundred and twenty seven patients were treated with the heater probe plus thrombin injection; the remainder received heater probe plus placebo injection. Re-bleeding developed in 19 (15%) of thrombin plus heater probe patients and 17 (15%) of placebo plus heater probe patients. Emergency surgery was necessary in 16 (13%) and 13 (11%) patients respectively. Eight patients (6%) in the thrombin group had adverse events compared

with four (3%) in the placebo group. Eight (6%) of thrombin plus heater probe patients and 14 (12%) of placebo plus heater probe patients died within 30 days ($p = 0.21$). These results suggest that the combination of thrombin and the heater probe does not confer additional benefit over heater probe and placebo as endoscopic treatment for bleeding peptic ulcer. This trial does not support the use of this combination of haemostatic therapy.

The Rockall scoring system can be used to predict mortality after gastrointestinal bleeding, but this score is less good at predicting re-bleeding. The utility of the system in patients who have undergone endoscopic therapy had not been studied. Rockall scores were calculated for all patients in the trial and the calibration and discriminative ability of the scoring system were assessed. The results show that after endoscopic therapy the score can be used to predict mortality but remains poor for the prediction of re-bleeding. Patients scoring six or greater should be regarded as "high-risk."

A detailed score was used to document the extent of comorbid disease in the trial patients. Outcome was closely related to overall score, higher scores being associated with re-bleeding, surgery and mortality. The impact of different comorbid conditions was assessed using logistic regression analysis. Neurological disease and malignancy were independently associated with re-bleeding. Surgery was required more commonly in patients with neurological and respiratory conditions, and neurological disease, respiratory conditions and renal failure were associated with death.

The heater probe is produced in large diameter (3.2mm) and small diameter (2.4mm) sizes. It has been suggested that the large diameter probe is most efficacious, although this is not supported by randomised trial evidence. The trial patients were analysed according to size of probe used and the outcomes suggest that the two heater probe sizes are equivalent.

Re-bleeding rates of 15-20% can be expected after initially successful endoscopic therapy. Accurate prediction of those patients at highest risk could allow for better use of intensive monitoring. An analysis of clinical and endoscopic factors showed that the presence of moderate or severe comorbid disease, an ulcer greater than 20mm in diameter and the presence of a posterior duodenal ulcer were independent predictors of re-bleeding.

Publications

Original Papers

NI Church and KR Palmer. Relevance of the Rockall Score in patients undergoing endoscopic therapy for peptic ulcer haemorrhage. European Journal of Gastroenterology & Hepatology 2001; 13(10): 1149-1152

NI Church, HJ Dallal, J Masson, NAG Mowat, DA Johnston, E Radin, M Turner, G Fullarton, RJ Prescott and KR Palmer. A randomized trial comparing heater probe plus thrombin with heater probe plus placebo for bleeding peptic ulcer. Gastroenterology 2003; 125(2): 396-404

NI Church, HJ Dallal, J Masson, NAG Mowat, DA Johnston, E Radin, M Turner, G Fullarton, RJ Prescott and KR Palmer. Validity of the Rockall scoring system following endoscopic therapy for bleeding peptic ulcer. Accepted for publication in Gastrointestinal Endoscopy

Reviews

NI Church, KR Palmer. Diagnostic and Therapeutic Endoscopy. Current Opinion in Gastroenterology 1999; 15: 504-508

KR Palmer, NI Church. Therapeutic Endoscopy for Upper Gastrointestinal Bleeding. CME Journal Gastroenterology, Hepatology & Nutrition 1999; 2(3): 75-78

NI Church, KR Palmer. Injection Therapy for Endoscopic Haemostasis. Ballieres Clinical Gastroenterology 2000; 14(3): 427-441

NI Church and KR Palmer. Ulcers and Non-variceal bleeding. Endoscopy 2003; 35(1): 22-26

Book Chapters

NI Church, KR Palmer. Acute non-variceal gastrointestinal haemorrhage: treatment. In: McDonald, Burroughs, Feagan (Ed), Evidence Based Gastroenterology and Hepatology. London: BMJ books 1999, pp 118-139. Update 2004 in press.

British Society of Gastroenterology Plenary session

Church NI, Dallal HJ, Masson J, Fraser A, Mowat NAG, Johnston DA, Fullarton G, Radin E, Turner M, Prescott R, Plevris J and Palmer KR. Endoscopic therapy for bleeding peptic ulcer; a randomized, controlled trial comparing heater probe plus human thrombin injection with heater probe plus placebo injection. Gut 2002; 50 (Suppl ii): A46

Other abstracts

Church NI, Dallal HJ, Kubba AK and Palmer KR. Relevance of the Rockall Score after endoscopic therapy for peptic ulcer haemorrhage. Gut 2000; 46(Suppl ii): A25.

Church NI, Nixon SJ and Palmer KR. Surgery for peptic ulcer – are trends still changing. Gut 2001; 48 (Suppl i): A38

Church NI, Dallal HJ, Masson J, Fraser A, Mowat NAG, Johnston DA, Fullarton G, Radin E, Turner M, Prescott R, Plevris J and Palmer KR. Ulcer haemostasis by the heater probe; bigger may not be better. Gut 2002; 50 (Suppl ii): A97

Chapter 1

Endoscopic therapy for peptic ulcer haemorrhage – a review of the literature

Introduction

Peptic ulcer is the commonest cause of acute non-variceal gastro-intestinal bleeding, accounting for approximately half of the cases (Fleischer, 1983). Other major causes such as gastroduodenal erosions, gastritis, oesophagitis, Mallory–Weiss tears, and vascular malformations are not usually life threatening and respond to conservative therapy.

Approximately 80% of patients who present to hospital because of acute upper gastrointestinal bleeding pursue a benign course without re-bleeding in hospital, and specific intervention is not required in these. The remaining 20% have severe bleeding due to erosion of a major artery. Most deaths from bleeding arise from this subgroup. The crude death rate from gastrointestinal bleeding has not significantly improved over five decades. Avery Jones (1947) reported a hospital mortality of 16% whilst a large audit of acute gastrointestinal bleeding performed in England in 1995 reported a very similar mortality of 14% (Rockall et al., 1995). This disappointing observation must, however, be tempered by the fact that the case mix of patients now admitted is very different to that of previous decades. For example, less that 2% of patients admitted with acute bleeding in 1947 were aged over 80 years whilst approximately a quarter of patients currently admitted are octogenarians. There is a close relationship between increasing age and hospital mortality: increasing age is inevitably associated with a high prevalence of chronic disease, rendering patients susceptible to complications following major haemorrhage.

Over the past 10 years the treatment of choice for bleeding peptic ulcer in appropriate patients has been endoscopic therapy, with surgical intervention being reserved for the failure of therapeutic endoscopy. Nevertheless, optimum management still relies very much on a team approach with appropriate use of drug therapy, endoscopic intervention, and surgery. Despite much evidence from randomised trials, the management of an individual patient still depends on clinical judgment; experienced endoscopists realise in some cases that attempts at endoscopic intervention are likely to be fruitless and that surgery is inevitable. Management may be best undertaken in a specialised "bleeding unit" in which the patient is treated using agreed protocols and guidelines with endoscopy undertaken once appropriate resuscitation has been achieved and with management decisions based upon endoscopic and surgical opinions. Relatively weak evidence derived from comparison of results in case series with historical controls suggests that this approach may achieve lower hospital mortality and more efficient use of resources than management by generalists working in conventional medical or surgical units (Holman et al., 1990; Sanderson et al., 1990).

Risk stratification

A number of scoring systems have been developed for quantifying the risk of re-bleeding and death following acute upper gastrointestinal bleeding (Rockall et al., 1996; Saeed et al., 1993; Pimpl et al., 1987; Garripoli et al., 2000; Guglielmi et al., 2002). A further report describes a system designed to predict a patient's need for

treatment of a bleeding episode (Blatchford et al., 2000). Scoring systems are particularly valuable in the setting of clinical trials and may be of less use in day-to-day clinical practice, although some units do employ modified scoring systems to facilitate clinical decision making.

The Rockall system was developed in the United Kingdom and published in 1996 (Rockall et al., 1996). Independent factors associated with a poor prognosis were identified from data derived from 4185 patients presenting with acute upper gastrointestinal bleeding whose clinical course was observed following hospital admission. The scoring system is summarised in Table 1.1. Whilst the Rockall risk scoring system performed well when tested in a cohort of patients subsequently managed in the same geographical area, until recently it has not been widely validated elsewhere. In a paper published in 1999 the Rockall score was shown to correlate well with observed mortality, but not re-bleeding, in a Dutch population (Vreeburg et al., 1999).

Table 1.1 The Rockall scoring system for risk of re-bleeding and death after admission to hospital for acute gastrointestinal bleeding

Variable	Score			
	0	1	2	3
Age	<60 yr	60–79 yr	≥80 yr	-
Shock	No shock	Tachycardia	Hypotension	-
	Systolic BP >100 Pulse <100	Systolic BP >100 Pulse >100	Systolic BP <100	
Co-morbidity	Nil major	-	Cardiac failure, ischemic heart disease, any major co-morbidity	Renal failure, liver failure, disseminated malignancy
Diagnosis	Mallory–Weiss tear, no lesion and no SRH	All other diagnoses	Malignancy of upper GI tract	-
Major SRH	None, or dark spot	-	Blood in upper GI tract, adherent clot, visible or spurting vessel	-

SRH, Stigmata of recent haemorrhage. Source: Rockall et al., 1996

As shown in Table 1.2, Rockall et al. showed a good correlation between the risk score, re-bleeding and hospital mortality. Deaths following admission to hospital because of acute gastrointestinal bleeding are rarely due to exsanguination. They are usually a consequence of postoperative complications when an urgent operation is undertaken, or due to deterioration of co-morbid conditions.

Table 1.2 Correlation between Rockall score and re-bleeding and mortality

Risk score	n	Re-bleed (%)	Mortality(%)
0	144	7 (5)	0 (0)
1	281	9 (3)	0 (0)
2	337	18 (5)	1 (0.2)
3	444	50 (11)	13 (3)
4	528	76 (14)	28 (5)
5	455	83 (24)	49 (11)
6	312	102 (33)	54 (17)
7	267	113 (44)	72 (27)
8+	190	101 (42)	78 (41)

Like the Rockall score, the Baylor bleeding score is derived from both clinical and endoscopic parameters. The score was developed in a much smaller cohort of 80 patients, but all were bleeding from high-risk peptic ulcers (Saeed et al., 1993) (Table 1.3).

Table 1.3 The Baylor bleeding score

Variable	Score					
	0	1	2	3	4	5
Age (years)	<30	30-49	50-59	60-69	-	≥70
Number of illnesses	0	1 or 2	-	-	3 or 4	≥5
Severity of illnesses	-	-	-	-	Chronic	Acute
Site of haemorrhage	-	-	-	-	Posterior duodenal bulb	-
Stigmata of haemorrhage	-	Clot	-	Visible vessel	-	Active bleeding

Source: Saeed et al 1993

Patients with a post endoscopy score of 10 or less were characterised as low risk, a score of greater than 10 conferring a high-risk status. The score was prospectively validated in a small sample of 49 patients treated endoscopically for bleeding peptic ulcer (Saeed et al., 1995). Re-bleeding in the low risk group was 0% compared with 31% in the high-risk group. The score did not accurately predict rates of surgery and mortality, but the numbers were too small to make statements concerning these end points. The Baylor bleeding score has recently been used to target elective repeat endoscopy and endoscopic therapy to patients with high-risk scores. This approach has been suggested to be more cost effective than a strategy of repeat endoscopy only when re-bleeding is clinically apparent (Spiegel et al., 2002).

The scoring system developed by Blatchford et al. (2000) differs from the other scores in two ways. Firstly, the system was designed to predict a need for intervention to treat bleeding, rather than to quantify the risk of re-bleeding or death. Secondly, the score does not include endoscopic findings as a component. Data were obtained from 1748 patients (the score development group) admitted following upper gastrointestinal bleeding in the west of Scotland. After logistic regression analysis a risk score was developed based on the admission haemoglobin, blood urea, pulse, systolic blood pressure, presentation with syncope, presentation with melaena, evidence of hepatic disease and evidence of cardiac failure. Intervention was defined as the requirement for a blood transfusion or endoscopic therapy or surgery to control bleeding. Increasing scores correlated with an increasing need for intervention in the score development group. A receiver operator curve was plotted for a subsequent

internal validation sample of 197 patients, and the score discriminated well with an area under the curve of 0.92 (95% CI 0.88-0.95). In the paper the numbers of patients requiring each intervention was not reported. External validation of this scoring system is required before it can be recommended for clinical use.

Specific therapy

For the 80% of patients who have relatively minor bleeding and who do not have major endoscopic stigmata of bleeding, supportive therapy including use of intravenous fluid and the management of co-morbidity (particularly cardiorespiratory disease) is sufficient.

Patients who present with clinical shock and who at endoscopy have an actively bleeding peptic ulcer (Figure 1.1) have an 80% risk of continuing to bleed or re-bleed in hospital (Bornman et al., 1985). Those who have a non-bleeding visible vessel (Figure 1.2) have a 50% risk of further haemorrhage (Griffiths et al., 1979). Patients who are found to have an adherent blood clot over the ulcer usually have an underlying high-risk lesion and should also be regarded as being at considerable risk of further haemorrhage in hospital. Patients who at endoscopy have a clean ulcer base or who have black or red spots are at very little risk of re-bleeding.

Figure 1.1 Active arterial bleeding from peptic ulcer

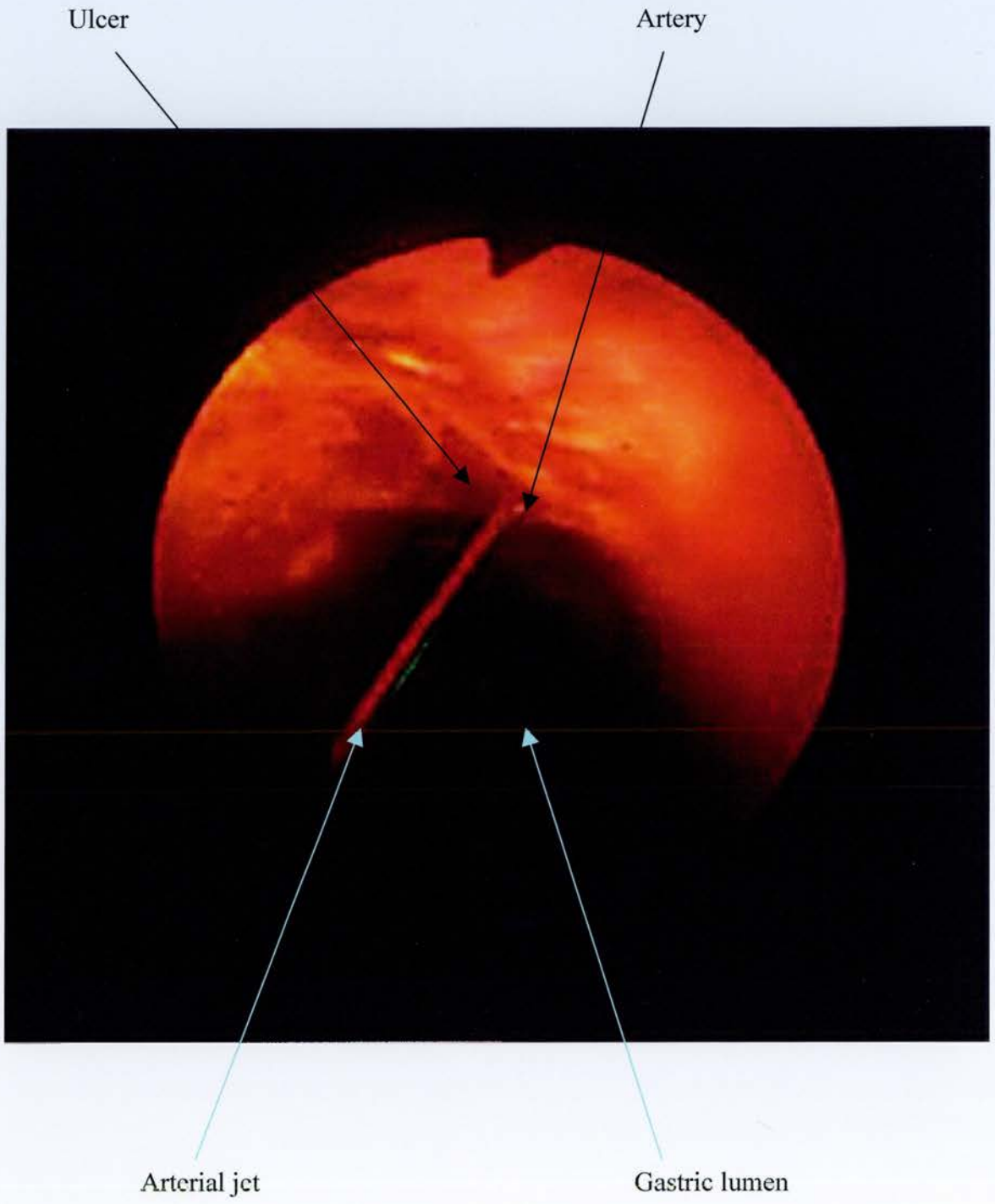
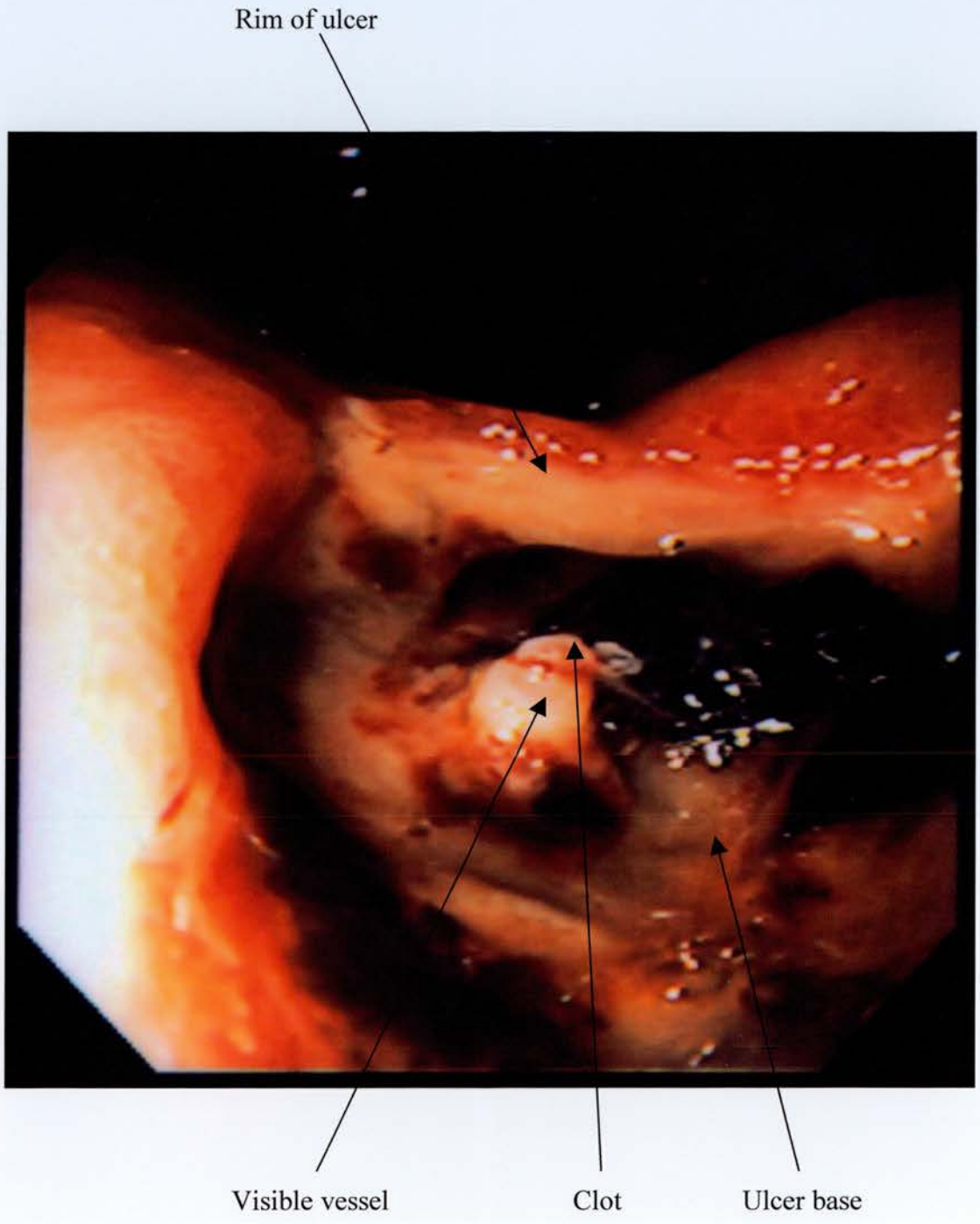


Figure 1.2 Non-bleeding visible vessel



It follows from these observations that patients with major endoscopic stigmata should be considered for specific haemostatic treatment and only such patients should be included in clinical trials of therapy for gastrointestinal bleeding. This section will consider those studies that include patients having a non-bleeding visible vessel, active haemorrhage, or adherent blood clot as entry criteria.

The specific non-surgical approaches to haemostasis are drug therapy and endoscopic therapy.

DRUG THERAPY

There are three principles underlying the use of drugs as agents which might stop active haemorrhage and prevent re-bleeding. The first of these is that the stability of a blood clot is poor in an acid environment (Patchett et al., 1989). Thus agents that suppress acid secretion, including H_2-receptor antagonists (H_2RA) and proton pump inhibitor (PPI) drugs might reduce re-bleeding. The second is that blood clot may be stabilised by decreasing fibrinolytic activity using agents such as tranexamic acid. The third approach is that, since major gastrointestinal bleeding is due to arterial erosion, reduction of arterial blood flow by agents such as somatostatin and octreotide could achieve haemostasis and prevent re-bleeding.

The efficacy of H_2RA in the management of acute upper gastrointestinal bleeding has been assessed in randomised trials (Walt et al., 1992; Collins and Langman, 1985). Unfortunately, no trial has shown benefit in terms of reduction of re-bleeding incidence or mortality.

Experience involving the use of PPIs is inconsistent, but recent evidence supports their use after endoscopic therapy. The largest trial involved 1147 patients who were randomised to receive intravenous, then oral omeprazole or placebo (Daneshmend et al., 1992). No significant difference in hospital mortality, operation rate or re-bleeding was demonstrated (Table 1.4). The study was not restricted to the high-risk patients who had endoscopic stigmata of recent haemorrhage. Accordingly, event rates were rather low in the placebo group, and this may have limited the power of the study to show a difference.

Khuroo et al. (1997) randomised 220 bleeding ulcer patients who had major endoscopic stigmata to receive high dose oral omeprazole or placebo. Although all patients had major stigmata of haemorrhage, 57% of patients were reported to have adherent clot in the ulcer base. Re-bleeding, the need for urgent surgery, blood transfusion, and mortality were all reduced in the patients receiving omeprazole (Table 1.5). The number of patients needed to treat with omeprazole to prevent one death was 25, and to prevent one operation was seven. This trial has been criticised because it included relatively young patients with relatively little co-morbidity and,

because endoscopic therapy was not administered to any patient. The observation that omeprazole reduced re-bleeding and surgery rates when no endoscopic therapy was performed suggested a beneficial effect of the PPI. This might be explained by the fact that the majority of patients in both groups had ulcers containing adherent clot.

Table 1.4 Omeprazole vs placebo for acute upper gastrointestinal bleeding

Outcome	Omeprazole	Placebo
All patients		
n	578	569
Re-bleed (%)	77 (15)	91 (17)
Operation (%)	56 (11)	57 (11)
Death (%)	35 (7)	29 (6)
Gastric ulcer		
n	97	93
Re-bleed (%)	26 (27)	23 (25)
Operation (%)	18 (19)	16 (17)
Death (%)	7 (7)	5 (5)
Duodenal ulcer		
n	149	164
Re-bleed (%)	32 (21)	47 (29)
Operation (%)	27 (18)	34 (21)
Death (%)	16 (11)	8 (5)

Source: Daneshmend et al., 1992

Table 1.5 Omeprazole vs placebo for bleeding peptic ulcer

Outcome	Omeprazole (n = 110)	Placebo (n = 110)	p
Re-bleed (%)	12 (11)	40 (36)	<0.001
Surgery (%)	8 (8)	26 (23)	<0.001
Transfusion (mean units)	2.3	4.1	<0.001
Death (%)	2 (2)	6 (6)	NS

Source: Khuroo et al., 1997

Two trials published back to back in the Scandinavian Journal of Gastroenterology examined the use of high dose intravenous omeprazole after endoscopic haemostasis (Schaffalitzky de Muckadell et al., 1997; Hasselgren et al., 1997). All patients had major peptic ulcer bleeding, but as in the trial by Khuroo half the patients had adherent clot as the reported stigma of haemorrhage. The conclusions were that intravenous omeprazole infusion for three days following endoscopic therapy improved outcome. Both trials used composite end-points which were complex and ill defined and were discontinued early due to an unexplained imbalance in mortality in one of the trials (Hasselgren et al., 1997), this reducing their overall impact.

Villanueva et al. (1995) randomised 86 patients following successful endoscopic haemostasis for peptic ulcer bleeding to either intravenous omeprazole or ranitidine. There were no differences between the groups for the end-points of re-bleeding, surgery or death. In contrast, a similar small trial by Lin and colleagues (1998) concluded that intravenous omeprazole was superior to cimetidine in terms of reduction of re-bleeding rates, but not those of surgery or death.

The most important trial was performed by Lau et al. (2000) and published in the New England Journal of Medicine. Two hundred and forty patients in whom endoscopic therapy for major ulcer bleeding had been successful were randomised. All patients had high-risk ulcers with active bleeding or non-bleeding visible vessels, and were treated by adrenaline injection followed by heater probe thermocoagulation. Adherent clots were removed to allow therapy to the underlying vessel. Patients then received either an 80mg bolus dose of intravenous omeprazole followed by an infusion of 8mg per hour for 72 hours or placebo. Re-bleeding rates, blood transfusion requirements and length of hospital stay were significantly reduced in the omeprazole group compared to placebo. There was a trend toward fewer operations and deaths in the omeprazole group, but this did not achieve statistical significance. (Table 1.6)

Table 1.6 Omeprazole vs placebo for bleeding peptic ulcer treated with endoscopic therapy

Outcome	Omeprazole (n = 120)	Placebo (n = 120)	p
Re-bleed (%)	8 (7)	27 (23)	<0.001
Surgery (%)	3 (3)	9 (8)	0.14
Transfusion (mean units +/-SD)	2.7 +/- 2.5	3.5 +/- 3.8	0.04
Length of stay < 5 days [number of patients (%)]	56 (47)	38 (32)	0.02
Death (%)	5 (4)	12 (10)	0.13

Source: Lau et al., 2000

Following the publication of the trial by Lau, the use of high dose intravenous PPI after successful endoscopic therapy for bleeding ulcer has become standard management in many centers in the UK and Europe. The 80mg bolus and 8mg per hour infusion regimen consistently raises intragastric pH above six for the majority of a 24 hour period (Hasselgren et al., 1998). It is not known, however, whether this optimum regimen is actually necessary following endoscopic therapy, and whether bolus intravenous or even oral PPI would suffice. Two small studies have attempted to answer these questions.

Udd et al. (2001) randomised 142 patients with ulcer bleeding to the high dose three-day intravenous omeprazole regimen or to a single daily bolus dose of 20mg for three days. Rates of re-bleeding (8% for high dose vs 12% for standard dose), surgery (4% vs 7%) and death (6% vs 3%) were comparable between the groups. Only 102 patients had required endoscopic therapy, and approximately 30% of patients had an ulcer with a black base only. Thus the number of high-risk ulcers in the trial was small, the event rates were low and its conclusions can be questioned.

The effect of oral Omeprazole following endoscopic therapy for bleeding peptic ulcer was studied by Javid et al. (2001). One hundred and sixty six patients with ulcers which were actively bleeding, had non-bleeding visible vessels or adherent clots were treated with a combination of 1:10,000 adrenaline plus 1% polidocanol injection. They were then randomised to receive oral Omeprazole 40mg bd or placebo. Six (7%) of the 82 patients in the omeprazole group re-bled compared with 18 (21%) of the 84 patients in the placebo group ($p = 0.02$). Surgery was required in

two patients in the omeprazole group and seven patients in the placebo group (p = 0.17). One death occurred in the omeprazole group compared to two in the placebo group. The results are comparable to those achieved by Lau with the high dose intravenous regimen (Lau et al., 2000). It should be noted, however that 40% of patients in this trial had ulcers with adherent clot, and the number of patients with high-risk lesions was therefore lower than that in the Hong Kong study. A further high quality trial comparing the use of intravenous and oral omeprazole in high-risk ulcer bleeding patients is now required.

The evidence now supports the use of PPIs following endoscopic haemostasis in patients with major peptic ulcer bleeding. All the trials show a trend towards reduction in re-bleeding in omeprazole treated patients although rates of surgery and mortality are not convincingly reduced. The trials are rather heterogeneous and few in number, this making meaningful meta-analysis difficult. Zed et al. (2001) performed an analysis of nine trials comparing PPIs with placebo or H_2RAs given after endoscopic therapy. The conclusion was that PPIs are superior to placebo and H_2RAs in terms of reduction of re-bleeding and surgery. Mortality was not reduced in the PPI groups. A second meta-analysis by Gisbert et al. (2001) included 11 trials and reached similar conclusions although the beneficial effect of PPI was found only to reduce re-bleeding. The group also noted that PPIs were most likely to be beneficial in patients with active bleeding and non-bleeding visible vessels, and in those patients who did not receive endoscopic therapy. It is not certain that use of PPIs saves lives, but the effect on surrogate markers such as re-bleeding, transfusion requirements, surgical operation and endoscopic intervention are convincing. There

do not appear to be significant hazards associated with the drugs and their cost in the context of an acutely bleeding patient is relatively minor.

Tranexamic acid

A meta-analysis of six controlled trials, which included 1267 patients, did not show a significant reduction in the rate of re-bleeding, but did show a reduction in the need for surgery and in mortality, which reached statistical significance (Henry and O'Connell, 1989) (Table 1.7). This meta-analysis included trials in which many patients did not have major endoscopic stigmata of bleeding. Therefore, the results may not be applicable to patient populations at greatest risk.

Table 1.7 Tranexamic acid for gastrointestinal bleeding – a meta-analysis

Outcome	Odds Ratio	95% CI	p
Re-bleeding	0.80	0.61–1.10	0.13
Operation	0.72	0.52–1.00	0.047
Death	0.60	0.40–0.89	0.01

Source: Henry and O'Connell, 1989

The largest study investigating the use of tranexamic acid was undertaken by the Nottingham group (Barer et al., 1983). Seven hundred and seventy-five patients presenting to hospital because of acute gastrointestinal bleeding were randomised to receive oral cimetidine, tranexamic acid or placebo. No significant difference in

bleeding or operation rates was demonstrated, but there was a rather surprising large difference in mortality. Mortality was 7.7% in cimetidine treated patients, 6.3% in tranexamic acid treated patients, and 13.5% in placebo. The mortality rate of 13.5% in the placebo treated group is greater than that expected for conservatively treated patients based on the results of other studies. Furthermore, other studies do not demonstrate benefit from the use of cimetidine. It is possible that more high-risk patients were inadvertently randomised to the placebo group in this study.

Somatostatin and octreotide

Somatostatin and its analogs have two actions which are theoretically valuable in the management of ulcer bleeding, namely inhibition of acid secretion and reduction of splanchnic blood flow. Mesenteric blood flow falls dramatically during infusions of somatostatin but it is not clear whether this is principally due to vasoconstriction of major blood vessels or peripheral arterioles.

There have been 14 controlled trials of somatostatin versus other therapy in the management of patients presenting with acute gastrointestinal bleeding (Sommerville et al., 1985; Magnusson et al., 1985; Basso et al., 1986; Corragio et al., 1984; Corragio et al., 1989; Galmiche et al., 1983; Saperas et al., 1988; Kayasseh et al., 1980; Antonioli et al., 1986; Tulassay et al., 1989; Torres et al., 1986; Wagner et al., 1983; Goletti et al., 1992; Christiansen et al., 1989). Two meta-analyses suggest that somatostatin but not octreotide has a primary haemostatic role and reduces the need

for surgical intervention (Jenkins et al., 1998; Imperiale and Birgisson, 1997). However, scrutiny of the relevant trials reveals many problems. Many of the studies were small and inclusion criteria varied widely from gastritis to major active bleeding.

The largest trial was reported by Sommerville et al. in 1985 (Table 1.8). Six hundred and thirty of 779 potentially eligible actively bleeding patients were randomised to receive somatostatin (a bolus of 250 mg followed by 250 mg hourly for 72 hours) or a placebo. No significant differences in re-bleeding, operation rate, and mortality were demonstrated between the treatment groups. The authors also reported the subgroup analysis of patients who had bled from gastric or duodenal ulcers. There were similar numbers of these in both active and placebo arms. Unfortunately the presence or absence of major stigmata of bleeding were not reported. The operation rate, mortality, and re-bleeding rates were similar in the two groups. However, a statistically significant difference in mortality in duodenal ulcer patients was demonstrated, with more actively bleeding patients dying. Although this is a large study, and patients were randomised early, the possible efficacy of somatostatin may have been difficult to demonstrate because of the inclusion of many patients whose prognosis was excellent because they had relatively trivial bleeding or, at the other end of the spectrum, inclusion of patients in whom operation and possibly death was inevitable because bleeding was so severe.

Table 1.8 Somatostatin vs placebo for acute gastrointestinal bleeding

Subgroup	Somatostatin	Placebo
All patients		
n	315	315
Re-bleed (%)	70 (22)	89 (28)
Operation (%)	35 (11)	34 (11)
Death (%)	31 (10)	25 (8)
Gastric ulcer		
n	57	57
Re-bleed (%)	18 (32)	21 (37)
Operation (%)	10 (18)	5 (9)
Death (%)	4 (7)	7 (12)
Duodenal ulcer		
n	77	81
Re-bleed (%)	21 (27)	31 (38)
Operation (%)	13 (17)	18 (22)
Death (%)	15 (19)	5 (6) *

Source: Sommerville et al., 1985

* $p < 0.02$.

A smaller study with contrasting results was reported by Magnusson et al. (1985) (Table 1.9). This trial only included patients who were clinically shocked due to active bleeding from peptic ulcers. Patients were randomised to receive somatostatin

or placebo infusion. Uncontrolled haemorrhage and need for surgical operation were commoner in placebo then somatostatin treated patients. However, the rates of mortality and re-bleeding were similar in both groups and the apparent difference in transfusion requirements was not statistically significant. This small study lacked the power to demonstrate a significant difference in mortality should a true difference exist.

Table 1.9 Somatostatin vs placebo for acute gastrointestinal bleeding

	Somatostatin	Placebo
n	46	49
Peptic ulcer bleeding	36	42
Stigmata of major bleeding	38	41
Continued bleeding (%)	8 (17)	16 (33)
Operation (%)	5 (11)	14 (29)
Re-bleeding (%)	6 (13)	5 (10)
Median transfused units	5.8	7.2
Death (%)	4 (9)	1 (2)

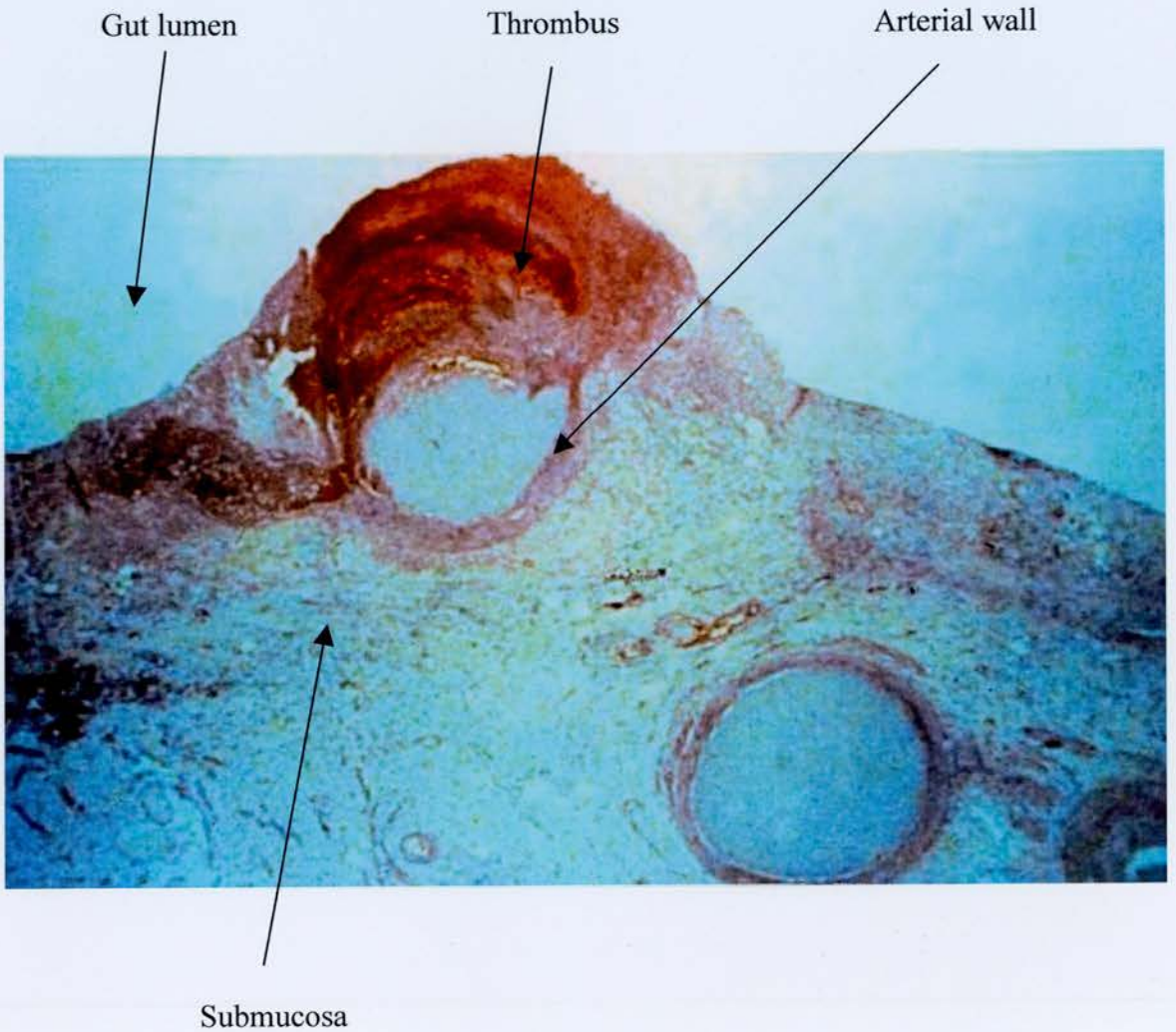
Source: Magnusson et al., 1985

Currently, the evidence for routine use of somatostatin is weak and further studies are needed before this agent can be recommended as routine therapy for non-variceal acute gastrointestinal bleeding.

Endoscopic stigmata of haemorrhage

Endoscopic stigmata of haemorrhage are seen in 20% of patients with peptic ulcer bleeding. Endoscopic therapy is only required when active bleeding, a non-bleeding visible vessel or adherent blood clot is present. Major ulcer bleeding is due to erosion of a submucosal artery. The affected artery may course for a considerable distance in the submucosa beneath the ulcer floor, and the potential endoscopic target is, therefore, sometimes relatively large. The majority of involved arteries are less than 2mm in diameter, and in 83% of cases there is arteritis and fibrinoid necrosis of the vessel wall, with associated aneurysmal dilatation of the artery in 52% (Swain et al., 1986). This pseudoaneurysm may bulge into the floor of the ulcer and is often associated with overlying blood clot. (Figure 1.3) Recanalised thrombus is seen in 24% of specimens. Less commonly, direct invasion of non-aneurysmal arteries occurs. The "visible vessel" which is the target for endoscopic injection thus comprises a true artery, a pseudoaneurysm or a clot plugging a defect. This area is clearly unstable and intervention may disrupt the fragile arterial wall, risking further major bleeding.

Figure 1.3 Pathology of the visible vessel



Mechanism of action of endoscopic therapy

Many endoscopic treatments have been used for ulcer bleeding. The endoscopist attempts to stop bleeding and prevent re-bleeding by causing a stable blood clot to form at the site of the eroded artery. Unfortunately neither examination of resected specimens or animal models define how this occurs. There are nevertheless three basic approaches to endoscopic therapy (Table 1.10).

Table 1.10 Endoscopic therapy

Modality	Type
Thermal	Argon laser
	Nd-YAG laser
	Heater probe
	Electrocoagulation
	Argon plasma coagulation
Injection	Adrenaline
	Sclerosants
	Alcohol
	Thrombin
	Fibrin glue
Mechanical	Haemoclips
	Staples
	Sutures

Thermal approaches involving laser, the heater probe and electrocoagulation by monopolar or bipolar probes attempt to induce thermocoagulation with thrombosis of the bleeding point. In experimental bleeding ulcers these approaches are more effective than injection treatments (Hepworth et al., 1998; Rutgeerts et al., 1989). Resected ulcers are rarely available for histological examination however, and the putative effects of injection therapy including thrombosis, endarteritis, oedema and acute inflammation are inherent features of chronic ulcer disease. Available animal models are based upon acute mucosal injury, and this has important differences to bleeding from peptic ulcers, which are the consequence of a chronic inflammatory process eroding a major artery. Studies based upon animal models which imply that injection therapy for ulcer bleeding is likely to be ineffective (Hepworth et al., 1998; Rutgeerts et al., 1989) are to be treated with skepticism. Clinical trials have conclusively shown that endoscopic therapy improves prognosis in ulcer bleeding patients, and it is probable that the available animal models are generally unsatisfactory.

The proposed mechanisms by which injection therapy stops ulcer bleeding and prevents re-bleeding are as follows:

1. Tamponade

Injection of fluid into the confined compartment of a rigid and fibrotic ulcer base may compress and therefore apply tamponade to the bleeding vessel. Trials by Lai et al. (1994) and Fleig (1994) support this hypothesis, reporting that endoscopic

injection of water was as effective at stopping bleeding as 1:10,000 adrenaline. These results are further supported by the study reported by Lin et al. (1993) who compared injection of normal saline, 3% NaCl solution, 50% glucose/water solution and pure alcohol in 200 patients with actively bleeding ulcers or non-bleeding visible vessels. There were no statistical differences between rates of initial haemostasis, re-bleeding, and surgery for any group. (Table 1.11) Larger injected volumes were required to achieve initial haemostasis in the saline and glucose/water groups, suggesting that tamponade was an important factor.

Table 1.11 Endoscopic injection for the arrest of peptic ulcer haemorrhage

	Normal Saline	3% NaCl	50% glucose/water	Pure Alcohol	p
n	50	50	50	50	-
Volume injected (ml) (Mean +/- SD)	15 +/- 8	16 +/- 9	9 +/- 5	3 +/- 2	Not Stated
Initial Haemostasis (%)	41 (82)	45 (90)	43 (86)	46 (92)	$p > 0.1$
Re-bleed (%)	3 (7)	11 (24)	6 (14)	5 (11)	$p > 0.1$
Surgery (%)	5 (10)	7 (14)	4 (8)	3 (6)	$p > 0.1$

Source: Lin et al., 1993

These results are challenged by those reported by Laine and Estrada (2002). In this study patients with high-risk ulcers were randomised to injection of normal saline (n= 48), or to bipolar electrocoagulation (n=52). Twenty nine percent of patients in the saline group re-bled compared with 12% of those treated with the BICAP. The saline patients required significantly more blood, but there were no differences in the duration of hospital stay or mortality.

The contribution of a tamponade effect is probably related to the degree of fibrosis in the ulcer base and the volume of fluid injected. It is not known whether injection can generate sufficient pressure to tamponade a bleeding artery. Any effect probably occurs at the time of injection, and the duration of action is unknown.

2. Vasoconstriction

Dilute adrenaline causes vasoconstriction. In both animal models of acute mucosal injury and in clinical trials, adrenaline has been shown to have a haemostatic benefit. Arteries within or adjacent to ulcers contain sufficient smooth muscle, with little atheroma (Swain et al., 1986) but vasoconstriction may be impaired by surrounding fibrosis. Injection of adrenaline is usually performed in a circumferential manner to cause constriction of arteries feeding the bleeding site. Endarteritis and arterial thrombosis do not occur as a direct result of adrenaline injection (Rajgopal et al., 1992), but large injected volumes (often up to 20ml) may have a significant tamponade effect.

The vasoconstrictive effects of injected adrenaline are likely to be short lived, although in experimental models vasoconstriction may persist for at least five minutes after injection (Rajgopal et al., 1992). It is possible that the temporary haemostasis occurring as the result of vasoconstriction may facilitate clot formation. It is also possible that other important effects, including alteration of platelet function (O'Brien, 1963) and stimulation of the coagulation cascade contribute to the efficacy of adrenaline injection.

3. Thrombosis

Both tamponade and vasoconstriction are presumed to be temporary effects, with a more permanent seal of the arterial defect supervening to prevent recurrent bleeding. Thrombosis is probably a consequence of tamponade and vasoconstriction, since in clinical trials adrenaline injection reduces re-bleeding in addition to achieving primary haemostasis. Direct formation of a clot using thrombin or fibrin glue is also effective. Pescatore et al. (1998) examined 20 specimens from patients who had required resection after injection treatment with fibrin glue. Resection occurred between six hours and nine days after injection. The ulcer was identified in 15 specimens, with no fibrin deposits found in three, sparse deposits in eight and large deposits in four. With increasing time after injection, the initial clot was replaced by fibroblast rich granulation tissue. This study gives some insights into events after fibrin glue injection, but as the specimens were all from patients in whom the injection therapy failed, its results can not be extrapolated to those patients who do not re-bleed. Further studies are needed.

4. Sclerosis

Sclerosant injections cause deep ulceration, tissue necrosis and venous thrombosis. Arteritis and arterial thromboses are infrequent (Rajgopal et al., 1992; Kubba et al., 1997). These histological effects occur some time after injection and it has been suggested that the main benefit of sclerosants is prevention of re-bleeding. As discussed elsewhere, there are concerns regarding their clinical use since in practice sclerosants provide no greater benefit in terms of re-bleeding than adrenaline injection alone, and because their use may cause extensive local necrosis (Rajgopal et al., 1992; Kubba et al., 1997; Randall et al., 1989).

5. Dehydration

Injection of absolute alcohol results in tissue dehydration with surrounding inflammation, necrosis, ulceration and vessel thrombosis (Randall et al., 1989). Trials using alcohol again show benefit over conservative therapy, but this is at the risk of considerable tissue damage.

The optimum volume of injection is not known. Small volumes of alcohol and sclerosants are required in order to minimise the risk of perforation. Much larger volumes of saline and adrenaline can be used without complication. In the trial by Lin et al. (1993) discussed above, the mean injection volume in the saline group was 15ml. Laine and Estrada (2002) injected a mean volume of 30ml. A further trial by Lin et al. (2002) compares large with relatively small volume injection. One hundred

and fifty six ulcer bleeding patients were randomised to injection of 5-10ml of adrenaline (the small volume group) or injection of 13-20ml (the large volume group). Re-bleeding occurred in 31% of the small volume patients compared with 15% in the large volume group. The other usual end-points were similar. The conclusion of this trial was that larger volume injections of adrenaline are safe and more likely to prevent re-bleeding than injection of a smaller volume.

Mechanical clips, staples, and sewing attempt to produce haemostasis by clamping the bleeding arterial lesion.

Clinical trials

Many clinical trials of endoscopic therapy for non-variceal bleeding have been published. The quality of these trials varies greatly. In general, the number of patients randomised in any one study is small and clinicians managing the patients have not been blinded to the type of endoscopic therapy.

Thermal methods

LASER PHOTOCOAGULATION

Lasers were the first endoscopic therapeutic modality shown to be effective in managing acute non-variceal gastrointestinal bleeding. Initial experience involved the use of argon lasers but it subsequently became clear that the tissue characteristics of thermal injury achieved by the Nd-YAG laser were more appropriate. In fact,

clinical trials showed little difference in outcome in series involving argon or Nd-YAG laser treatment. There have been three randomised trials comparing argon laser therapy and conservative therapy for bleeding peptic ulcer (Vallon et al., 1981; Swain et al., 1981; Jensen et al., 1984) and a further nine trials of Nd-YAG laser treatment (Swain et al., 1986; Krejs et al., 1987; Rhode et al., 1980; Rutgeerts et al., 1982; MacLeod et al., 1983; Homer et al., 1985; Trudeau et al., 1985; Buset et al 1988; Matthewson et al., 1990) (Table 1.12). Most of these studies show that laser treatment significantly reduced the rates of re-bleeding, transfusion requirement, and operation rate. One trial showed significant improvement in hospital mortality (Swain et al., 1986). However, experience has not been universally positive with laser treatment. It is revealing to compare the best performed study with a large American multicenter study, published in the New England Journal of Medicine. Swain et al. (1986) randomised 138 patients to laser treatment or conservative therapy. He personally undertook all endoscopic examinations and treatments and was responsible for the clinical management of the treated subjects. His study showed significant reduction in re-bleeding, need for emergency surgery, and mortality in laser treated patients. In contrast Krejs et al. (1987) randomised a similar number of patients to laser therapy or to conservative treatment. Patients treated by laser tended to have a poor outcome compared to control patients. It was apparent in this study that endoscopic therapy was undertaken by a large number of endoscopists who varied in their expertise. Of all therapeutic endoscopic modalities, laser therapy is the most difficult to use. Even in Swain's hands up to 17% of ulcers could not be treated. The method is a "no touch" one and an awkwardly placed duodenal ulcer within a deformed duodenum may be extremely difficult to adequately treat. Thus

the results in the hands of relatively inexperienced therapeutic endoscopists, each performing few procedures, was likely to have been variable. Furthermore, the patients included in this trial were managed in many units, rather than by a single "bleeding team".

Endoscopic laser therapy has been found to be relatively safe with few complications; in particular, gastrointestinal perforation has been rare. However, since the technique is difficult, relatively expensive and because other approaches are at least as effective, laser therapy for peptic ulcer bleeding is no longer used.

Table 1.12 Nd–YAG trials for bleeding peptic ulcer

Study	Group	n	Re-bleed (%)	Surgery (%)	Mortality (%)
Swain, 1986	Laser	70	7 (10)	7 (10)	1 (1.4)
	Control	68	27 (40)	24 (35)	8 (12)
Krejs, 1987	Laser	85	19 (22)	14 (16)	1 (1.2)
	Control	89	18 (20)	15 (17)	1 (1.1)
Rhode, 1980	Laser	62	37 (59)	8 (13)	15 (24)
	Control	43	24 (57)	18 (41)	12 (27)
Rutgeerts, 1982	Group 2: L	46	3 (7)	1 (2)	6 (13)
	Group 2: C	40	6 (15)[a]	5 (13)	6 (15)
	Group 3: L	17	3 (18)	2 (12)	2 (12)
	Group 3: C	26	8 (31)	6 (23)	4 (15)
MacLeod, 1983	Laser	21	6 (29)	5 (24)	1 (5)
	Control	24	8 (33)	8 (33)	2 (8)
Homer, 1985	Laser	17	3 (18)	—	0 (0)
	Control	25	8 (32)	—	2 (8)
Trudeau, 1985	Laser	18	2 (11)	1 (5)	2 (11)
	Control	15	6 (40)	4 (26)	5 (33)
Buset, 1988	Laser	42	10 (24)	3 (7)	1 (2)
	Control	46	17 (37)	2 (4)	2 (4)
Matthewson, 1990	Laser	44	9 (20)	9 (20)	1 (2)
	Heater probe	57	16 (28)	13 (22)	6 (10)
	Control	42	18 (43)	13 (30)	4 (9)

[a]6 of 31 where bleeding stopped.

Rutgeerts group 2: active non-spurting bleeding.

Rutgeerts group 3: inactive bleeding with stigmata of recent haemorrhage.

The heater probe transmits preset amounts of energy to the bleeding point via a Teflon tipped catheter. A powerful water jet is used to clean the ulcer base, help visualize the bleeding point and prevent the probe sticking to the bleeding point. Haemostasis is achieved by coaptive coagulation, using both tamponade and the application of heat. Best results are said to be achieved using large sized probes. There have been three trials in which the heater probe has been compared to conservative therapy (Fullarton et al., 1989; Jensen et al., 1988; Jaramillo et al., 1993). All showed benefit in terms of further bleeding, and surgery, and one published only in abstract form (Jensen et al., 1988) demonstrated a trend towards reduction in mortality (Table 1.13).

The heater probe is "user friendly". Its capacity to apply thermal energy by tangential application and its powerful water jet are particular advantages. Perforations have occurred following treatment, although these are unusual, and are generally of the order of 1% (Wong et al., 2002). Questions remain concerning the amount of energy that should be applied. In general, medium power settings (20 - 30 Joules) are used but it is not possible to be prescriptive concerning the total amount of energy that should be given. Most authorities consider that treatment should be continued until active haemorrhage is stopped and until the treated area is blackened and cavitated.

Table 1.13 Heater probe for gastrointestinal bleeding

Study	Group	Re-bleed (%)	Surgery (%)	Mortality (%)
Fullarton, 1989	HP (n = 20)	0 (0)	0 (0)	0 (0)
	Sham (n = 23)	5 (22) *	3 (13) **	0 (0)
Jensen, 1988	BICAP	44	33	3
	HP	22 ***	3 ***	3
	Nil	72	41	9
	n (total) = 94			
Jaramillo, 1993	HP (n = 51)	5 (10)	3 (6)	0 (0)
	Control (n = 50)	13 (26) ****	7 (14)	1 (2)

* $p = 0.05$.

** p not stated.

*** $p < 0.05$.

**** $p = 0.03$.

HP, heater probe

BICAP, bipolar electrocoagulation.

Monopolar electrocoagulation uses a metal ball-tipped probe. An electrical circuit is completed by a plate attached to the patient. Application of energy is rather haphazard and perforations and a death were reported in early series. Consequently this device is no longer used. Bipolar electrocoagulation is based upon transmission of electrical energy between adjacent electrodes. The BICAP has eight separate electrodes over its surface. Early studies from the United Kingdom involving small numbers of patients showed no benefit for active treatment compared to conservative therapy. Subsequently however, trials from the United Kingdom and the USA showed that primary haemostasis, re-bleeding, the need for surgery and transfusion requirements were all improved by bipolar electrocoagulation compared to conventionally treated patients (O'Brien et al., 1986; Laine, 1987; Brearly et al., 1987; Laine, 1988) (Table 1.14). The efficacy of the heater probe and BICAP are comparable and the two modalities have similar low complication rates (Wong et al., 2002; Papp, 1987).

Table 1.14 Electrocoagulation for gastrointestinal bleeding

Study	Group	n	Re-bleed (%)	Surgery (%)	Mean units transfused
O'Brien, 1987	Bipolar probe	101	17 (17) *	7 (7)	4.6 **
	Nil	103	34 (33)	10 (10)	7.3
[a]Laine, 1987	MPEC	21	—	3 (14) ***	2.4 †
	Sham	23	—	10 (43)	5.4
Brearley, 1987	Bipolar probe	20	6 (30)	—	—
	Nil	21	8 (38)	—	—
[b]Laine, 1988	MPEC	37	7 (19) ‡	3 (8)	1.6 ‡
	Sham	37	15 (41)	11 (30)	3.0

* $p = 0.01$.

** $p = 0.13$.

*** $p = 0.049$.

† $p = 0.002$.

‡ $p < 0.05$.

MPEC, multipolar electrocoagulation.

[a]Study included ulcers, Mallory–Weiss tears, and vascular malformations.

[b]Study was restricted to ulcers with non-bleeding visible vessels. See also Jensen, 1988 Table 1.13

ARGON PLASMA COAGULATION

This procedure is based upon coagulation through a jet of argon gas. Relatively superficial thermal damage is achieved. The method is particularly applicable to mucosal and superficial bleeding lesions, and its final role may be in dealing with vascular malformations such as gastric antral vascular ectasia. One small trial has shown that argon plasma coagulation is comparable in efficacy to heater probe therapy for ulcer haemostasis (Cipolletta et al., 1998). A second trial compared the argon plasma coagulator with combination injection of adrenaline and polidocanol (Skok et al., 2001). Again the two approaches were equally effective. Nevertheless the tissue damage characteristics of argon plasma coagulation are less than ideal for managing arterial bleeding, and it will probably prove to be less appropriate for managing peptic ulcer bleeding than contact methods.

CONCLUSIONS

Thermal methods of haemostasis were shown to be superior to conservative management in two meta-analyses. In a meta-analysis, involving thermal contact devices, laser and injection therapy performed by Cook et al. (1992) the odds ratio for prevention of re-bleeding was 0.48 (95% CI 0.32–0.76); and for avoidance of surgery was 0.47 (95% CI 0.27–0.80). Similarly, in the study of Henry and White (1988), the odds ratio for prevention of bleeding was 0.32 (95% CI 0.22–0.41) and for the avoidance of surgery was 0.31 (95% CI 0.19–0.43). Thermal contact methods (heater probe and bipolar coagulation) are technically easier to undertake than laser

techniques. There are insufficient data to determine whether the heater probe is better than the BICAP.

The safety profile of thermal modalities is generally very good. Perforations are unusual and treatment induced exacerbation of bleeding is not usually clinically important.

Injection therapy

Injection treatment is simple to perform and is the cheapest available haemostatic modality. A number of injection materials have been studied and it is difficult to prove that any one of these is superior to others.

DILUTE ADRENALINE

In 1988 Chung et al. reported a controlled trial in which patients with active ulcer bleeding were randomised to receive endoscopic injection with 1:10,000 adrenaline or to conservative treatment. Primary haemostasis was achieved in all injected patients and the need for subsequent urgent surgery was significantly reduced (Table 1.15). Re-bleeding occurred in 24% of injected patients, suggesting that although dilute adrenaline did stop active bleeding, its effects were temporary.

Table 1.15 Adrenaline for gastrointestinal bleeding

Outcome	Adrenaline (n = 34)	Conservative (n = 34)
Primary haemostasis (%)	34 (100)	—[a]
Surgery (%)	5 (15)	14 (41)
Mortality (%)	3 (9)	2 (6)

[a] 20 patients stopped bleeding spontaneously.

Source: Chung et al., 1988

It seemed logical to combine an injection of adrenaline with that of an agent which might cause permanent sealing of the bleeding arterial defect. For this reason a series of trials were undertaken in which adrenaline injection was combined with a range of sclerosants.

The results of trials in which a combination of adrenaline plus sclerosants were compared to conservative therapy are summarised in Table 1.16 (Panes et al., 1987; Rajgopal and Palmer, 1991; Balanzo et al., 1988; Oxner et al., 1992). All showed that active bleeding stopped more rapidly in treated patients, that re-bleeding rates were less and that the need for a surgical operation was reduced. No single trial, however, was powerful enough to determine whether mortality was affected. The meta-analysis by Cook et al. (1992) did show a modest reduction in mortality, although this only achieved statistical significance for laser therapy.

Table 1.16 Adrenaline plus sclerosants for gastrointestinal bleeding

Study	Group	n	Re-bleed (%)	Surgery (%)	Mortality (%)
Panès, 1987	Adr + Pol + Cim	55	3 (5)	3 (5)	2 (4)
	Cim	58	25 (43)	20 (34)	4 (7)
Rajgopal, 1991	Adr + Eth	56	7 (13)	6 (11)	2 (4)
	Nil	53	25 (47)	13 (25)	3 (6)
Balanzo, 1988	Adr + Pol	36	7 (19)	7 (19)	—
	Nil	36	15 (42)	15 (42)	—
Oxner, 1992	Adr + Eth	48	8 (17)	4 (8)	4 (8)
	Nil	45	21 (47)	8 (18)	9 (20)

Adr, adrenaline; Pol, polidocanol; Eth, ethanolamine; Cim, cimetidine.

SCLEROSANTS

The sclerosants that have been studied are polidocanol, 5% ethanolamine oleate, and 3% sodium tetradecyl sulphate. There are no controlled trials in which outcome has been assessed in patients randomised to sclerosant injection versus conservative therapy. Several trials compared the efficacy of sclerosants with other endoscopic therapies. Benedetti et al. (1990) showed similar efficacy for polidocanol and thrombin injection in patients presenting with a range of bleeding lesions. Strohm et al. (1994) randomised patients to one of four treatment arms (fibrin glue, 1% polidocanol, dilute adrenaline or adrenaline plus polidocanol) and showed no

advantage for any one approach. Rutgeerts et al. (1989) showed no difference in outcome for patients treated by polidocanol or Nd-YAG laser therapy. In general these studies suffer from the problem of small sample size, and they probably lacked statistical power.

A series of case reports have documented complications of injection by sclerosant (Levy et al., 1991; Loperfido et al., 1990), particularly perforation and necrosis of the upper gastrointestinal tract. These complications did not occur following adrenaline injection and indeed the latter seems remarkably safe. Fears concerning the possible systemic affects of circulating adrenaline have not translated into cardiovascular mishaps. Since complications are mainly due to sclerosant injection, it was important to confirm the importance of combining the sclerosant with the adrenaline injection. Whilst the logic of attempting to induce endarteritis using sclerosants was reasonable, experiments in animals did not demonstrate that this could be achieved by injection using ethanolamine or absolute alcohol (Rajgopal et al., 1992). Three trials compared the efficacy of injection by adrenaline alone versus a combination of adrenaline plus a sclerosant (Villanueva et al., 1993; Choudari and Palmer, 1994; Chung et al., 1996). As shown in Table 1.17, these three studies did not show that combination treatment was superior to injection by adrenaline alone. No study has directly compared outcome in patients randomised to dilute adrenaline or to a sclerosant. Since the addition of sclerosants to an injection of adrenaline offers no proven advantage over injecting adrenaline alone, and because sclerosants have the potential to cause significant local complications following injection, they should no longer be employed as part of the injection treatment regimen.

Table 1.17 Adrenaline vs adrenaline plus sclerosant in gastrointestinal bleeding

Study	Group	n	Primary haemostasis	Re-bleed (%)	Surgery (%)	Transfusion (units +/– range)	Mortality (%)
Villanueva, 1993	Adr + Pol	33	32	7 (21)	5 (15)	2	1 (3)
	Adr	30	29	3 (10)	4 (13)	2	2 (7)
Choudari, 1994	Adr + Eth	52	—	7 (14)	4 (8)	8	0 (0)
	Adr	55	—	8 (15)	4 (7)	9	1 (2)
Chung, 1993	Adr + Alc	79	75	6 (8)	9 (11)	2 (0–23)	7 (9)
	Adr	81	79	9 (11)	12 (15)	3 (0–20)	4 (5)

Adr, adrenaline; Alc, alcohol; Eth, ethanolamine; Pol, polidocanol.

The efficacy of injecting absolute alcohol into bleeding ulcers has been examined in several clinical trials. Two of these (Pascu et al., 1989; Lazo et al., 1992) (Table 1.18) randomised patients to alcohol injection or to conservative therapy and showed benefit in terms of reduction in re-bleeding rates and need for surgical intervention.

Table 1.18 Alcohol vs conservative therapy for gastrointestinal bleeding

Study	Group	n	Re-bleeding (%)	Surgery (%)	Mortality (%)
Pascu, 1989	Alcohol	65	1 (2) *	1 (2)*	2 (3)
	Conservative	78	17 (22)	17 (22)	10 (13)
Lazo, 1992	Alcohol	25	2 (8) **	1 (4) ***	—
	Conservative	14	8 (57)	7 (50)	—

* $p = 0.0007$.

** $p < 0.001$.

*** $p < 0.05$.

In a prospective randomised comparative trial, Lin et al. (1993) reported that alcohol injection stopped active bleeding and prevented re-bleeding in 86% of patients whose ulcers were injected, and this result was similar to the proportion of bleeding ulcers responding to injection with 3% sodium chloride, 50% dextrose, or normal saline. Only one small study (Chiozzini et al., 1989) has attempted to compare the efficacy of alcohol with dilute adrenaline injection but this lacked statistical power to demonstrate possible differences in the efficacy of these interventions.

The evidence that alcohol stops active bleeding and prevents re-bleeding is stronger than that for the sclerosants. Unfortunately, the potential for adverse effects is probably higher for alcohol than for adrenaline. Deep ulcers commonly follow alcohol injection and perforations have occurred (Nakagawa et al., 1989).

Whilst alcohol injection is an effective haemostatic therapy, current evidence suggests that the magnitude of its effect is probably similar to that achieved by injection with adrenaline alone. Because of its propensity for causing adverse effects, alcohol injection is not recommended as treatment for ulcer bleeding.

FIBRIN GLUE AND THROMBIN

The most attractive endoscopic approach is to directly cause blood clot formation by injecting thrombogenic substances. In the 1980s small trials examined the efficacy of bovine thrombin and showed little benefit compared to other modalities.

In 1996 Kubba et al. reported a comparison of endoscopic injection therapy using a combination of adrenaline plus human thrombin with dilute adrenaline injection alone (Table 1.19). A proportion of randomised patients had active bleeding at the time of randomization, while the remainder had non-bleeding visible vessels. Re-bleeding and mortality were significantly reduced in the group receiving combination therapy compared to patients receiving adrenaline alone. The number of patients needed to be treated with combination therapy rather than adrenaline alone to prevent one death is approximately 14. Paradoxically, no statistically significant differences

in the need for surgical operation and the overall rate of haemostasis were demonstrated. Indeed, deaths in this study all occurred, as is usually the case, in patients who had significant co-morbidity. There were no complications. Although this was not a direct comparison of adrenaline versus thrombin, it did strongly suggest that human thrombin is an effective modality.

Table 1.19 Adrenaline plus thrombin vs adrenaline alone for gastrointestinal bleeding

Outcome	Adrenaline + Thrombin (n = 70)	Adrenaline alone (n = 70)
Re-bleed (%)	3 (4)	14 (20) *
Transfusion (units)	7	5
Surgery (%)	3 (4)	5 (7)
Mortality (%)	0 (0)	7 (10) **

* $p < 0.005$.

** $p < 0.013$.

Source: Kubba et al., 1996

In a large multicenter European study (Rutgeerts et al., 1997) (Table 1.20) 850 patients were randomised to endoscopic injection with dilute adrenaline plus a single injection of fibrin glue, to adrenaline and repeated injection of fibrin glue given at daily intervals according to the discretion of the endoscopists, or to adrenaline plus 1% polidocanol. Fibrin glue is a mixture of fibrinogen and thrombin which is injected through a double-channeled endoscopy needle. Re-bleeding rates were

lowest in patients treated by repeated injection, and serious re-bleeding requiring major blood transfusion or surgical operation, was significantly reduced in patients receiving repeated injections of glue compared to the polidocanol treated group. A total of seven perforations occurred in this study and these were distributed equally amongst the treated modalities.

Table 1.20 Adrenaline plus fibrin glue vs adrenaline plus polidocanol for gastrointestinal bleeding

Outcome	Adr + rep FG (n = 284)	Adr + single FG (n = 285)	Adr + Pol (n = 281)
Re-bleed (%)	41 (16)	51 (19)	58 (21) *
Transfusion (units)	3.7	3.2	3.3
Surgery (%)	9 (3)	13 (5)	13 (5)
Perforation (%)	2 (1)	2 (1)	3 (1)
30-day mortality (%)	12 (4)	15 (5)	13 (5)

* $p < 0.036$.

Adr, adrenaline; FG, fibrin glue; Pol, polidocanol.

Source: Rutgeerts et al., 1997

Finally, a small study (Heldwein et al., 1996) which compared a combination of adrenaline plus fibrin glue with adrenaline plus Nd-YAG laser therapy did not show a difference in outcome, but this study lacked sufficient statistical power.

Although no direct comparisons have been made of injection therapy using thrombin alone versus other single agents, the impression gained from the trial evidence is that the use of thrombogenic agents confers significant benefit in terms of the usual endpoints. Acute complications occur infrequently. Although thrombin has been derived from pooled plasma, viral transmission has not been reported. Furthermore, no adverse effects have been apparent in terms of systemic coagulation.

Human thrombin is not currently commercially available. It is relatively inexpensive at £35 per vial, although more costly than adrenaline at £1 per vial.

CONCLUSION

Injection therapy is effective and safe. The optimum injection regimen should probably include dilute adrenaline, which stops active haemorrhage. Re-bleeding rates may be reduced by the addition of agents such as thrombin or a thrombin–fibrinogen mixture. Sclerosants and alcohol should not be used since there is no evidence that they are beneficial and they increase the risk of serious complications.

Comparison of injection and thermal treatments

A number of small trials have compared injection with thermal therapies, and as in most studies in this field, numbers are small. In general, the two modalities appear to have equivalent efficacy.

Six trials have compared heater probe with injection (Lin et al., 1988; Lin et al., 1990; Chung et al., 1991; Choudari et al., 1992; Saeed et al., 1993; Llach et al., 1996) (Table 1.21). The two trials reported by Lin et al. (1988, 1990) showed that heater probe treatment was more effective in achieving primary haemostasis. These authors noted the heater probe to be better when ulcers were difficult to approach, as it can be applied tangentially. They also found the water jet to be useful in spurting bleeding. It may be argued that alcohol is a less appropriate injection therapy than adrenaline, which may account for the apparent superiority of the heater probe in these studies. This view was supported by the findings of Chung et al. (1991). They concluded that heater probe and adrenaline were equally effective, but that initial haemostasis was more easily achieved with adrenaline. Choudari et al. (1992) compared the heater probe with adrenaline plus ethanolamine and found no differences between the modalities. The remaining two trials by Saeed et al. (1993) and Llach et al. (1996) support this conclusion. Laine (1990) showed that electrocoagulation and injection with ethanol were equivalent, although the size of this trial was suboptimal.

Two trials involved the Nd-YAG laser. Carter et al. (1994) compared laser with adrenaline and Pulanic et al. (1995) in a much larger trial, compared laser with polidocanol. Neither showed a difference in outcome.

Current evidence does not allow a conclusion to be drawn on whether injection or thermal treatment is superior.

Table 1.21 Comparison of heater probe with injection therapy

Study	Group	n	Primary haemostasis (%)	Re-bleed (%)	Surgery (%)	Mortality (%)
Lin, 1988,	HP	42	42 (100)	5 (12)	—	—
	PA	36	29 (81)	6 (22)	—	—
Lin, 1990	HP	45	44 (98) *	8 (18)	3 (7) **	1 (2) †
	PA	46	31 (67)	2 (7)	2 (4)	0
	Control	46	—	—	12 (26)	7 (15)
Chung, 1991	HP	64	53 (83) ‡	6 (11)	14 (22)	4 (6)
	Adr	68	65 (96)	11 (17)	14 (21)	2 (3)
Choudari, 1992	HP	60	—	9 (15)	7 (12)	3 (5)
	Adr + Eth	60	—	8 (13)	7 (12)	2 (3)
Saeed, 1993	HP	39	35 (90)	4 (10)	—	—
	Ethanol	41	33 (81)	5 (12)	—	—
Llach, 1996	HP	53	—	3 (6)	2 (4)	1 (2)
	Adr + Pol	51	—	2 (4)	2 (4)	1 (2)

* $p = 0.0004$.

** $p = 0.0024$ ($p = 0.027$ between control and HP; $p = 0.012$ between PA and HP).

† $p = 0.002$ ($p = 0.031$ between control and HP; $p = 0.018$ between control and PA).

‡ $p < 0.05$.

HP, heater probe; PA, pure alcohol; Adr, adrenaline; Eth, ethanolamine; Pol, polidocanol.

Combination of injection and thermal treatments

The mechanisms leading to haemostasis associated with thermal treatment and injection therapy may differ, providing a rationale for combining a thermal modality with injection treatment. Currently, only one small study has shown overall benefit from use of such a combination. This trial by Lin et al. (1999) used the gold probe, a bipolar coagulation probe containing an injection needle in the centre. Using this device heat and injection therapy may be applied without removing the probe from the ulcer. Ninety six patients were included in this randomised trial, injection alone, coagulation alone or combination therapy being applied to 32 patients each. Re-bleeding rates were lower in the combination group compared to the injection alone and coagulation alone groups (7% vs 36%, p=0.01 and 7% vs 30%, p=0.04 respectively), and volume of blood transfused in the combination group was significantly lower. Although this trial indicates a beneficial outcome following combination endoscopic therapy, the number of patients in each group was small, this limiting the impact of the conclusion. A much larger trial is required.

A further encouraging trend relates to a finding within a study reported by Chung et al. (1997) This study involved randomization of appropriate ulcer bleeding patients to injection therapy using 1: 10,000 adrenaline or to a combination of adrenaline plus the heater probe (Table 1.22). Although there was no overall difference in outcome between patients randomised to either arm, a post hoc subgroup analysis did reveal positive findings. Sixty patients had active spurting haemorrhage from large ulcers, and within this group the primary haemostatic effect of both treatments was similar.

However, the need for operation was significantly reduced in the group treated by heater probe and injection. The number of endpoints was small and this observation from subgroup analysis requires confirmation in further trials.

Table 1.22 Adrenaline plus heater probe vs adrenaline alone for gastrointestinal bleeding

Outcome	Adrenaline + Heater Probe	Adrenaline alone
Overall		
n	136	134
Primary haemostasis (%)	135 (99)	131 (98)
Re-bleed (%)	5 (4)	12 (9)
Transfusion (units)	3	2
Surgery (%)	8 (6)	14 (11)
Mortality (%)	8 (6)	7 (5)
Subgroup with spurting haemorrhage		
n	32	28
Primary haemostasis (%)	31 (97)	25 (89)
Re-bleed (%)	2 (6)	6 (21)
Transfusion (units)	4	5
Surgery (%)	2 (6)	8 (29) *
Mortality (%)	Not stated	Not stated

* $p = 0.03$.

Source: Chung et al., 1997

Mechanical clips

The haemoclip was first used for non-variceal bleeding by Japanese investigators in the early 1970's (Hayashi et al., 1975). The device has gained favour, particularly in Japan, and is the endoscopic method most analogous to under-running an ulcer at operative surgery. Three large case series (Binmoeller et al., 1993; Yokohata et al., 1996; Nagayama et al., 1999) support haemoclips as a safe and effective method for the treatment of bleeding peptic ulcer and there are five prospective randomised trials of reasonable size (Chung et al., 1999; Cipoletta et al., 2001; Lin et al., 2002; Lin et al., 2003; Gevers et al., 2002).

Chung IK et al. published a prospective randomised trial comparing haemoclips with adrenaline injection in 1999. One hundred and twenty four patients with actively bleeding ulcers or ulcers with vessels were included. Forty one patients were treated with haemoclips, 41 with adrenaline and 42 with a combination of the two. Re-bleeding occurred in 2.4%, 14.6% and 9.5% respectively. Three patients had complications, all in the adrenaline group.

Cipoletta et al. (2001) randomised 113 patients with endoscopic stigmata of haemorrhage to heater probe thermocoagulation or to application of haemoclips. A mean of three clips per patient were used with up to six being required in some cases. Re-bleeding was dramatically reduced in the haemoclip group with rates in the clip and heater probe groups of 1.8 % and 21 % respectively. There were no complications.

The two previous trials suggested clips to be effective, with re-bleed rates below 3% in the clip only groups. Three subsequent studies however have been less encouraging. Eighty patients were randomised to heater probe thermocoagulation or to placement of haemoclips in the trial by Lin et al. (2002). Primary haemostasis was achieved in only 85% of patients in the clip group versus 100% of those treated with the heater probe. Re-bleed, surgery and mortality rates were no different. Subsequently, Lin et al. (2003) compared 46 ulcer bleeding patients treated by haemoclip placement with 47 patients in whom heater probe thermocoagulation and adrenaline injection were used. The rate of primary haemostasis was lower in the haemoclip group (95.1% vs 100%, $p>0.1$). Re-bleeding, surgery and mortality rates were equivalent. Gevers et al. (2002) performed a similar trial to Chung et al. (1999) in which 101 patients were randomised to injection with adrenaline and polidocanol, haemoclip application or a combination of the two. The overall failure rate was significantly higher in the haemoclip alone group when compared with the injection and combination groups (34%, 6% and 25% respectively, $p=0.01$).

The major difficulty with haemoclip placement occurs when ulcers are difficult to reach and tangential application is required. Initial clip applicators resulted in problems with clip alignment, but a rotary applicator has now been developed. Further problems arise when clips are applied to the fibrous base of a chronic ulcer, as in this situation it may not be possible to adequately compress the bleeding vessel. In the trial by Lin et al. (2002) a surveillance endoscopy was performed at 72 hours following therapy. Haemoclips had been successfully placed in 31 patients, but at 72 hours the clip was still attached to the ulcer base in only 10 patients. This could have

accounted for the disappointing performance of the clip group, and perhaps clips with a more powerful clamping mechanism would improve the efficacy of the device. Further trials with improved clips are required.

Endoscopic therapy for ulcers with adherent blood clot

There is debate concerning what should be done with blood clot which is tightly adherent to an ulcer base. It is possible to deliver endoscopic therapy around the base of, and through an adherent clot. The efficacy of this approach is not known. To remove a clot seems counter-intuitive in the situation of acute bleeding, but to leave it in situ prevents accurate categorisation of stigmata of haemorrhage, and may prevent correct application of endoscopic therapy. Lin et al. (1996) showed that when clot is tightly adherent after washing for 10 seconds with Water Pik irrigation, the re-bleed rate is 25%. Factors independently associated with re-bleeding in this situation were the presence of shock, co-morbid disease and haemoglobin less than 10 g/dl. Bleau et al. (2002) published a small trial in which patients with adherent clot were randomised to pre-injection with adrenaline followed by clot removal and thermocoagulation of a visible vessel (n=21), or to medical therapy (n=35). The patients in the endoscopic therapy group had a significantly lower re-bleeding rate (5%) compared with those in the medical therapy only group (34%), although the numbers were small. A similar but very small trial (32 patients) has been reported by Jensen et al. (2002). The results were similar, with re-bleeding rates of 0% in the clot removal and endoscopic therapy group versus 35% for those treated with medical therapy only. These trials suggest that clot removal and therapy to the underlying

stigmata is a safe and effective strategy. A further trial should now randomize patients to clot removal and endoscopic therapy, or to endoscopic therapy delivered through the clot.

Elective repeat endoscopic therapy

It is not yet clear whether electively repeating endoscopy and haemostatic therapy in the absence of clinical or endoscopic signs of re-bleeding is a useful strategy. There are six trials which include patients receiving repeated endoscopic therapy (Rutgeerts et al., 1997; Pescatore et al., 2002; Messman et al., 1998; Villanueva et al., 1994; Saeed et al., 1996; Chiu et al., 2003) and four of these have specifically addressed the question of the efficacy of endoscopic re-treatment (Messman et al., 1998; Villanueva et al., 1994; Saeed et al., 1996; Chiu et al., 2003). The trial by Pescatore et al. (2002) reported no clear benefit from the use of an elective repeat endoscopy approach. A similar conclusion was reached by Messmann et al. (1998) in a study of 105 patients who had required endoscopic therapy for bleeding ulcers. Patients were randomised to daily repeat endoscopy with re-treatment of persistent stigmata, or to close observation. There was no difference between the groups for any of the usual end-points. In contrast to these results, Rutgeerts et al. (1997) reported a clear positive trend towards reduction in re-bleeding in patients treated with programmed repeat endoscopic therapy. Villanueva et al. (1994) randomised 104 patients in whom endoscopic haemostasis had been achieved following injection of adrenaline, to repeat endoscopy or to observation. There were trends towards a better outcome in

the repeat endoscopy group but statistically significant reductions in re-bleeding, surgery and mortality were not demonstrated.

There are two trials suggesting that repeat endoscopic therapy significantly reduces re-bleeding rates. The very small trial by Saeed et al. (1996) included only 40 patients, but Chiu et al. (2003) randomised 194 patients following endoscopic haemostasis using adrenaline injection and heater probe thermocoagulation. One hundred patients underwent a scheduled repeat endoscopy and 35 of these required further endoscopic therapy. The remaining 94 patients were observed closely. All patients received intravenous omeprazole 40mg twice daily for 72 hours following endoscopy. The mean total volume of adrenaline injected in the repeat endoscopy group was 11.1ml compared with 9.1ml in the control group ($p=0.008$). The mean total joules of heater probe therapy in the two groups were 95.3 and 110.2 respectively. Re-bleeding rates were significantly lower in the repeat endoscopy group compared to the control group (5% vs 14%, $p=0.034$). There was also a trend towards reduction in the requirement for surgery (1% vs 6%, $p=0.05$). Mortality rates were similar in the two groups.

Two meta-analyses examining the above trials have been published (Marmo et al., 2003; Chiu et al., 2003). Both suggest that elective repeat endoscopy significantly reduces re-bleeding, but has no beneficial effect on the rates of surgery or mortality.

Potential complications of repeat endoscopic therapy including sedation related cardiorespiratory adverse events, and heater probe related perforation have not been

reported. In many cases repeat endoscopic therapy is not required at the time of second look endoscopy, and a cost-benefit analysis of a policy of elective repeat endoscopic therapy would be desirable. Currently, the total number of patients studied is small, but the available evidence indicates that elective repeat endoscopic therapy may be beneficial in patients at high-risk of re-bleeding or surgery. Repeat endoscopy should also be considered in cases where the endoscopist is not convinced that adequate haemostasis has been achieved at the time of the initial endoscopy.

Failure of endoscopic therapy

It may be argued that endoscopists can adversely affect outcome in patients who fail endoscopic therapy. Repeated unsuccessful therapeutic endoscopy, large blood transfusion, and delayed surgical operation in those who ultimately fail attempted endoscopic haemostasis all increase the risk of death. Unfortunately, we cannot predict who will fail and who will respond to endoscopic therapy. Seven analyses (Villanueva et al., 1993; Choudari et al., 1994; Hsu et al., 1994; Brullet et al., 1996 (Gut); Brullet et al., 1996 (Gastrointest Endosc); Chung IK et al., 2001; Wong et al., 2002) have shown that the presence of active bleeding, large ulcer size, an ulcer situated in the posterior duodenum, the presence of significant co-morbid disease, shock and a haemoglobin less than 10g/dl are factors associated with failures of therapy. However, even in the highest risk group of patients, who present with active spurting haemorrhage from large posterior duodenal ulcers, endoscopic haemostasis can be achieved in approximately 70% of patients (Choudari et al., 1994). Currently it is not possible to accurately define the subgroup of patients in whom endoscopic

therapy should not be attempted. What is clear is that patients who have actively bleeding, large posterior duodenal ulcers are at very high-risk of requiring urgent operation.

Policy concerning re-bleeding after failed endoscopic therapy has been examined by Lau et al. (1999). Of 3473 patients admitted with bleeding peptic ulcers, 1169 underwent endoscopic therapy in an attempt to achieve haemostasis. Primary haemostasis was achieved in a remarkable 98.5% of patients. One hundred of these re-bled after endoscopic therapy and 92 were randomised to endoscopic re-treatment or to emergency surgery. The characteristics of the two groups of patients were similar, including the median transfusion requirements before randomization. Endoscopic re-treatment consisted of a combination of adrenaline injection plus the heater probe. Overall, more complications occurred in the group randomised to surgery and there was no significant difference in 30-day mortality between the two groups (Table 1.23). This paper suggests that endoscopic re-treatment rather than immediate, urgent operative surgery should be considered in patients who re-bleed after endoscopic haemostatic therapy.

Table 1.23 Repeat endoscopic therapy vs surgery for patients who re-bleed

Outcome	Endoscopic therapy	Surgery
n	48	44
Transfusion (units)	8	7
Complications (no. of pts) (%)	7 (15)	16 (36) *
Mortality (30-day) (%)	5 (10)	8 (18)

* $p = 0.03$.

Source: Lau et al. (1999)

Endoscopic therapy: summary

Endoscopic therapy for non-variceal haemorrhage is safe and effective, and should be used in the 20% of patients who have major endoscopic stigmata of recent haemorrhage. Combination therapy may produce the best results, but there is no definitive proof that this is the case. It is possible that combination therapy is the best approach for patients with active, spurting haemorrhage. Thermal haemostasis is effective using either the heat probe or multipolar electrocoagulation. No injection agent has been convincingly shown to be superior to dilute adrenaline solution. Injection of larger volumes may improve outcome. The haemoclip requires further development. Re-bleeding should be treated first by further endoscopic intervention, although clinical judgment should dictate when urgent surgery is required for specific high-risk cases.

Intravenous infusion of proton pump inhibitor drugs is recommended following successful endoscopic haemostasis. There is little evidence that other drug therapies are effective.

Chapter 2

A randomised controlled trial comparing heater probe plus thrombin with heater probe plus placebo for bleeding peptic ulcer: Patients and Methods

Introduction

This thesis is based upon a clinical trial which examined the hypothesis that combination injection and heater probe therapy is superior to heater probe therapy alone in preventing re-bleeding after major peptic ulcer haemorrhage. A previous clinical trial showed that injection of human thrombin into the bleeding ulcer is a highly effective haemostatic treatment (Kubba et al., 1996), and others have also shown that injection of agents which lead to blood clot formation improves outcome in these patients (Rutgeerts et al., 1997). Thrombin was therefore used as an injection material, combining this with the heater probe.

No previous clinical trials of endoscopic therapy had been placebo controlled and many studies are therefore open to criticism. In this double blind study patients were randomised to receive either a combination of heater probe plus thrombin injection or heater probe plus placebo injection.

Patients

Patients were recruited from four Scottish regions between November 1996 and January 2001. The participating centres were as follows:

1. Edinburgh (Western General Hospital, Royal Infirmary, St. John's Hospital)
2. Aberdeen (Aberdeen Royal Infirmary)
3. Dundee (Ninewells Hospital)
4. Glasgow (Gartnavel General Hospital)

All patients presenting with significant haematemesis and/or melaena were considered for inclusion into the trial. All had peptic ulcers with major endoscopic stigmata comprising active bleeding or a non-bleeding visible vessel. At endoscopy the bleeding point was vigorously washed to remove adherent clot and facilitate full endoscopic visualisation. In 20 cases blood clot was initially adherent. In all of these, snares and washing catheters were used to reveal a non-bleeding visible vessel in 19 and active, spurting haemorrhage in one. In order to be eligible for inclusion into the study at least one additional clinical risk factor from age over 60 years, haemoglobin less than 10 g/dl, the presence of shock (defined as a pulse rate greater than 100 beats per minute or a systolic blood pressure less than 100 mmHg or both) and significant co-morbid disease was necessary. Co-morbid disease was classified and graded as shown in Table 2.1. Arbitrary scores of 1 to 3 were applied to disease in major organ systems depending on the disease severity, and the sum of the scores for each category produced the final co-morbid disease score for each patient. Rockall scores (Rockall et al., 1996) were calculated for all patients (see Chapter 1).

Exclusion criteria comprised the use of anticoagulant drugs, the presence of a coagulopathy, known severe chronic liver disease, advanced malignancy, a history of severe reactions to blood products and pregnancy.

Table 2.1 Classification of co-morbid disease

Category	*Score*
Liver/Gastrointestinal	
Inactive or mild liver disease, inactive inflammatory bowel disease (IBD)	1
Cirrhosis/portal hypertension, moderate IBD, short bowel syndrome, chronic pancreatitis	2
Liver failure, encephalopathy, severe active IBD, acute pancreatitis	3
Cardiovascular	
Stable angina, previous myocardial infarction (MI), hypertension, mild peripheral vascular disease (PVD)	1
Bad angina, mild congestive cardiac failure, valvular heart disease, moderate PVD	2
Recent MI (within 4 weeks), severe heart failure, severe PVD	3
Respiratory	
Mild asthma/ chronic obstructive airways disease (COAD)	1
Asthma/COAD chronic but no exacerbation, chest infection, pulmonary embolus at least 2 months previously	2
Respiratory failure, recent PE, pneumonia, severe exacerbation of asthma/COAD	3
Diabetes	
Well controlled diabetes	1
Diabetic with complications	2
Ketoacidosis	3
Arthritis	
Minor conditions including mild rheumatoid arthritis (RA), gout, symptomatic osteoarthrosis	1
Less severe RA but requiring medication	2
Severe RA, connective tissue disease	3
Neurological	
Previous stroke, Parkinson's disease receiving treatment, other chronic neurological disease	1
Stoke within 6 months with residual disability, recent transient ischaemic episode, severe dementia	2
Stroke within 4 weeks, severe neurological condition with disability	3
Renal	
Mild renal failure/impairment, mild renal disease	1
Chronic renal failure, chronic renal disease	2
Acute renal failure, dialysis, transplant	3
Cancer	
Early/mild (e.g. prostatic/cervical/bladder), chronic leukaemias and non-malignant tumors	1
Limited spread or treated cancer	2
Terminal cancer, disseminated cancer, acute leukemia	3
Recent operation (within 4 weeks) or trauma	
Minor operations, minor burns/trauma	1
Recent major operation, severe burns/trauma	3

Randomisation

Written consent was obtained, either from the patient or in some cases from a close relative, prior to endoscopy. Endoscopy was undertaken following resuscitation, and patients found to have peptic ulcers with appropriate stigmata of haemorrhage were entered into the trial. All patients were treated with the heater probe followed by injection of trial material, which was contained in consecutively numbered boxes. These were allocated using randomised permuted blocks of length ten to contain vials of human thrombin or matching placebo. Allocation was concealed and the trial investigators were blinded to the contents of the vials of trial injection material.

Endoscopic Therapy

Endoscopy was carried out using Olympus forward viewing gastroscopes (Q200, XQ240, XQ10, XQ20 or 2T200). All procedures were carried out by myself or by senior endoscopists experienced in the use of the heater probe and injection therapy.

The Olympus heater probe unit (HPU/HPU 20) with 2.4mm or 3.2mm diameter probes (CD20Z, CD10Z, CD120U, CD110U) was used. All probes were calibrated by the manufacturer to produce the same heating characteristics. Firm tamponade was applied before application of 20 to 30J pulses. The probe was applied circumferentially around non-bleeding vessels and then to the vessel itself. Two to four pulses were delivered at each position. Application was continued until active bleeding (if present) stopped and the bleeding point was blackened and cavitated.

Injection was carried out using a disposable 4mm injection needle (Keymed Ltd, Southend upon Sea, UK). Human thrombin 1000 iu or placebo was presented in apparently identical vials of dry powder. The powder was reconstituted with sterile water, producing a 3.5 - 4ml injection volume after priming the injection needle. This was injected in 1ml aliquots into the bleeding point following application of the heater probe.

Each box contained two vials to allow for a second injection should this prove necessary in the event of re-bleeding.

THROMBIN

Human thrombin was produced by the Scottish National Blood Transfusion Service (SNBTS) and was initially derived from cryoprecipitate obtained from voluntary UK blood donations. When the new-variant Creutzfeldt Jacob Disease crisis developed in the UK in 1997, human thrombin derived from UK donors was withdrawn due to the possibility of transmission of the disease by plasma products. Thereafter thrombin was fractionated in an identical manner from plasma donated in the USA and Germany. The extract was subjected to two virus inactivation steps comprising an in-process solvent/detergent step using 1% Tween 80 and 0.3% Tri N Butyl Phosphate at 25°C for at least 6 hours, followed by dry terminal heat treatment at 80°C for 72 hours. This has been shown to inactivate a range of enveloped and non-enveloped viruses (Bennet et al., 1993; Horowitz et al., 1993; Rizza et al., 1993). Despite the virus inactivation steps in the manufacturing process thrombin injection carries a theoretical risk of transmission of Parvovirus B19 and Hepatitis A. In order to

monitor the safety of thrombin injection, 10ml clotted samples of blood were taken from all patients prior to endoscopy and six months after injection. These samples were analysed for antibodies to Parvovirus B19 and Hepatitis A to monitor for seroconversion. As part of the SNBTS standard safety procedures, post-endoscopy samples were tested for Hepatitis B and Hepatitis C antibodies and Hepatitis B surface antigen. In the event of positive post-endoscopy tests for hepatitis B or C, the pre-endoscopy samples were tested. This approach avoided testing the entire patient group for hepatitis B and C.

PLACEBO

Matching placebo was produced by the Protein Fractionation Center in Edinburgh. Each vial contained all the constituents of the SNBTS thrombin concentrate except for thrombin itself, which was replaced by human albumin. Specifically this comprised an isotonic solution containing sodium citrate, sodium chloride, sodium gluconate and 1.9g/l human albumin. The appearance and viscosity of the active and placebo solutions were identical, and none of these constituents are known to have vasoconstrictor activity.

Follow Up

Following endoscopy patients received proton pump inhibitor drugs and, if appropriate H. Pylori was eradicated by a seven-day course of antibiotics combined with a proton pump inhibitor drug. Following endoscopic therapy clinical management decisions were left to the admitting physicians or surgeons at the

respective units. Endoscopy was only repeated during the admission if re-bleeding was suspected.

The primary end point of the trial was:

Re-bleeding, defined as the passage of fresh haematemesis or melaena associated with the development of shock or a fall in haemoglobin concentration by at least 2 g/dl in 24 hours. This was diagnosed by clinicians who were in charge of all management decisions but had no knowledge of whether patients had received thrombin or placebo.

Secondary end points were:

1. Need for urgent surgery to prevent exsanguination. The decision to undertake surgery was made by the parent unit on the basis of the clinical condition of the patient.
2. 30-day mortality.
3. Volume of blood transfused.
4. Duration of hospital admission.

Re-bleeding was confirmed whenever possible by further endoscopy. If major stigmata were found, heater probe application and injection of the second vial of reconstituted test material were undertaken. Surgery was performed if active

bleeding could not be controlled or when further gastrointestinal haemorrhage occurred.

Patients were followed up by out-patient review or telephone call 30-days after the initial bleed. All patients were contacted six months after injection and in those who consented repeat blood samples were taken to ensure no virus transmission had occurred.

Statistical Design

The trial was designed to have an 80% power to detect a difference between re-bleeding rates of 5% and 16% at the 5% level of significance. It was assumed that approximately 16% of patients would re-bleed after heater probe plus placebo, based upon previous published trials (Choudari et al., 1992; Lin et al., 1990; Chung et al., 1991). It was calculated that 120 patients would be required in each arm. Differences in proportions were analyzed using the χ^2 test with Yates' correction. Length of hospital stay was compared using the t-test after logarithmic transformation. Blood transfusion requirements were compared using the Wilcoxon Rank Sum Test. In order to monitor the safety of the trial for participants, the mortality rates were compared at intervals of approximately 75 patients and it was predetermined that the data would be examined in detail if differences were significant at a level of 0.01. Statistical analysis was carried out using the SPSS version 10 statistical package.

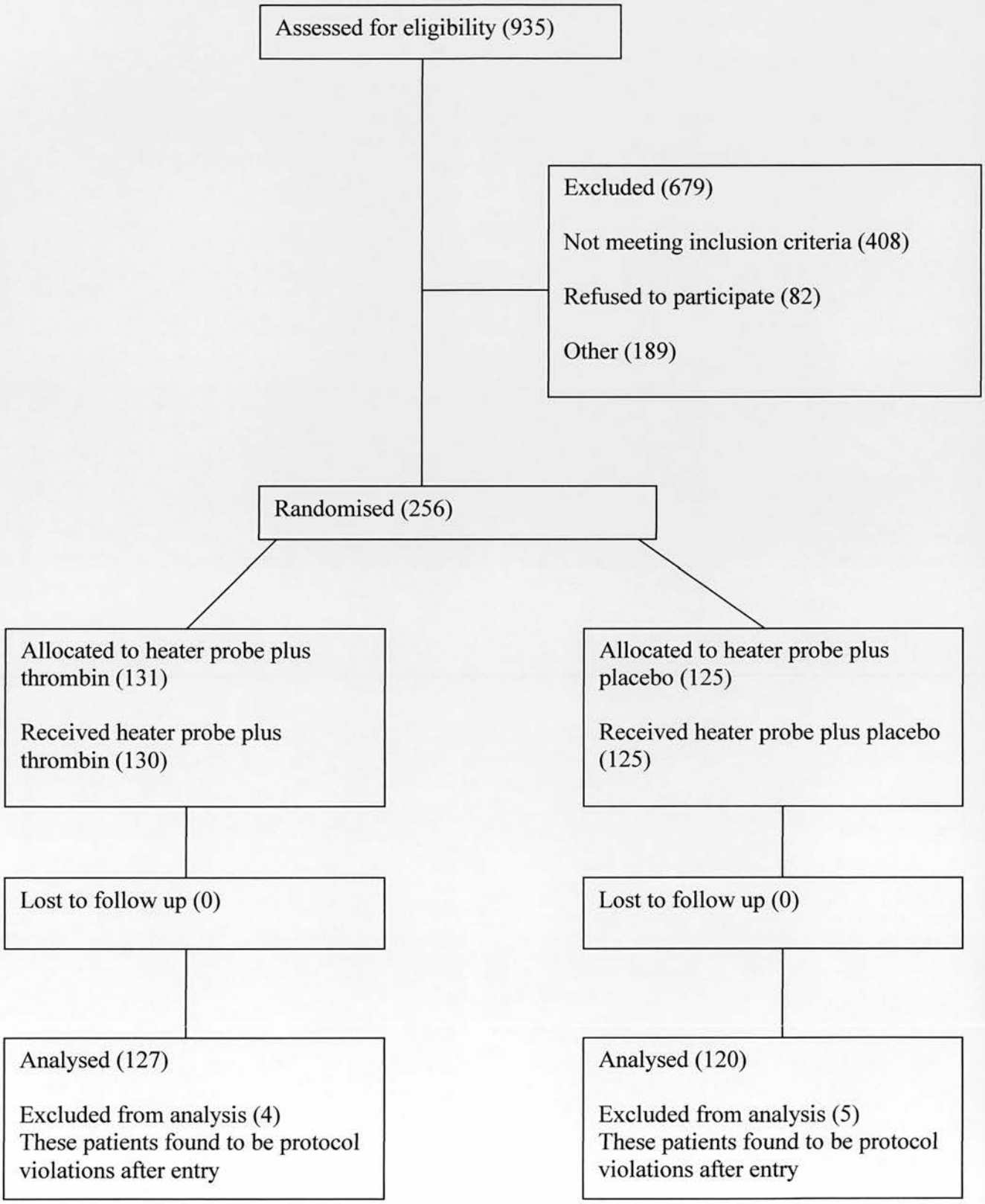
Chapter 3

A randomised controlled trial comparing heater probe plus thrombin with heater probe plus placebo for bleeding peptic ulcer: Re-bleeding and Mortality

Inclusions and exclusions

Nine hundred and thirty five patients met the initial entry criteria and were considered for entry into the trial. Of these 679 were excluded, primarily due to the absence of major stigmata of haemorrhage in the peptic ulcer. Two hundred and fifty six patients were entered into the trial. One hundred and thirty one patients were randomised to receive thrombin injection and the remaining 125 patients to placebo injection. As the use of the heater probe was common to both arms of the trial, the groups are subsequently referred to as the 'thrombin' and 'placebo' groups. Nine patients were withdrawn because of major protocol violations. In the thrombin group three patients had received adrenaline injection in addition to the trial therapy and one did not receive the injection of thrombin. Of these, two patients had further bleeding requiring surgery. A gastric carcinoma was found in one case, and the patient died two weeks later after conservative management at home. Two patients from the placebo group had more than one ulcer requiring endoscopic therapy, one was found to be participating in another trial, one received adrenaline in addition to the trial therapy and one was taking anticoagulant drugs. Surgery was required for definitive control of bleeding in both patients with multiple ulcers, and both had died within 30-days due to cardiorespiratory complications. The other three patients had an uncomplicated course. All these patients were removed from the final analysis before breaking the randomisation code (Figure 3.1).

Figure 3.1 Trial flow diagram



The characteristics of the patients groups are shown in table 3.1. One hundred and eight patients were treated by myself, the remaining 64 patients from Edinburgh being entered by Dr H Dallal. Fifty nine patients were treated by Professor NAG Mowat in the bleeding unit at Aberdeen Royal Infirmary. In Dundee, 13 patients were treated by Dr D Johnston. Three patients were entered by Mr G Fullarton at Gartnavel General Hospital in Glasgow. The principal research fellows (Dr Dallal initially, followed by myself) were based in Edinburgh, and consequently, the majority of patients entered into the trial were from this region. A number of eligible patients from the other sites were not included due to the lack of a full time researcher, but the disparate recruitment from the centres merely resulted in a prolongation of the time required to randomise sufficient patients, and would not have affected the results of the trial.

The groups were well matched for age, gender, co-morbid disease, shock, haemoglobin, type and site of ulcer, stigmata of haemorrhage and therapy applied. Analysis for statistical differences between the groups was not required as the patients were randomised at entry into the trial (Prescott et al., 1999). The use of the co-morbid disease score and the Rockall score is discussed in subsequent chapters.

Table 3.1 Patient characteristics

	Thrombin	Placebo
n	127	120
Median age (range)	72 (22-94)	70 (20-92)
Sex (M:F)	84:43	84:36
Shock (%)	81 (64)	75 (63)
Median co-morbid disease score (Range)	2 (0-10)	2 (0-12)
Median Rockall score (Range)	6 (3-10)	5 (3-10)
Median Hb concentration (Range) g/dl	9.4 (6.2-18.1)	9.4 (4.0-14.8)
Number taking NSAIDs (%)	31 (24)	24 (20)
Median ulcer size (range) mm.	10 (1-50)	10 (2-50)
Gastric ulcer (%)	48 (38)	38 (32)
Duodenal ulcer (%)	72 (57)	71 (59)
Oesophageal ulcer (%)	3 (2)	6 (5)
Stomal ulcer (%)	4 (3)	5 (4)
Spurting (%)	8 (6)	5 (4)
Oozing (%)	41 (32)	40 (33)
Total active bleeding (%)	49 (39)	45 (38)
Non-bleeding visible vessel (%)	78 (61)	75 (63)
Median number of joules applied (range)	120 (30-420)	125 (45-300)
Median volume of injected fluid (range) ml	3.5 (2-7)	3.5 (3.5-7)

Primary haemostasis was not achieved in four patients from each group. Five of these patients had active bleeding at the time of endoscopy. In three patients with non-bleeding visible vessels torrential bleeding was induced by endoscopic therapy.

The outcome of therapy is shown in Table 3.2. Fifteen percent of patients re-bled in each group. The relative risk of re-bleeding in patients receiving thrombin compared to placebo was 1.06 (95% CI, 0.58-1.93). The difference in absolute risk of re-bleeding between the groups was 0.8% (95% CI, – 8% - 9.6%) in favour of placebo.

Table 3.2 Outcome of treatment (all patients)

	Heater probe plus thrombin	Heater probe plus placebo
n	127	120
Primary haemostasis (%)	123 (97)	116 (97)
Re-bleed (%)	19 (15)	17 (15)
Emergency surgery (%)	16 (13)	13 (11)
30-day mortality (%)	8 (6)	14 (12)
Permanent haemostasis (%)	104 (82)	99 (83)
Median units transfused (range)	3 (0-32)	2 (0-35)
Total units transfused	470	433
Median duration of admission (range), days	5 (2-82)	5 (1-121)

Endoscopic re-treatment was carried out in seven patients randomised to thrombin and in eight patients receiving placebo injections. Re-treatment was successful in five patients from the thrombin group, although two of these subsequently required emergency surgery for re-bleeding. In the placebo group re-treatment succeeded in four patients, one of whom subsequently underwent surgery. In eighteen patients repeat endoscopic treatment was not clinically appropriate. Two patients died shortly after bleeding recurred; one died from exsanguination before treatment could be instigated, and another very elderly frail patient was kept comfortable and not subjected to any definitive treatment. The remaining 16 patients had extreme bleeding and the referring clinicians felt that urgent surgery, without repeat endoscopy, was necessary.

The numbers of patients requiring emergency surgery for bleeding were similar in the two groups. For thrombin compared to placebo the relative risk of surgery was 1.16 (95% CI, 0.58 – 2.31). The difference in absolute risk of surgery was 1.8% (95% CI, – 6.2% - 9.8%) in favour of placebo.

Permanent haemostasis was achieved in 104 patients (82%) in the thrombin group and 99 patients (83%) in the placebo group.

Median blood transfusion requirements were similar in the two groups. ($p = 0.69$) The duration of admission (analysed after logarithmic transformation due to the markedly skewed distribution) was also similar in the two groups ($p= 0.67$).

A subgroup analysis was performed in patients with active arterial bleeding. Table 3.3 shows outcome in relation to particular stigmata and demonstrates similar outcome in both treatment groups. The difference in mortality in patients with active bleeding did not achieve statistical significance ($\chi^2_c = 1.4$, $p = 0.24$).

Adverse events occurred in eight patients receiving thrombin and in four treated with placebo (Table 3.4). Three perforations occurred; these exclusively developed in the thrombin group and each was confirmed by laparotomy. One of these probably occurred before endoscopy; in the other two cases perforation was an unexpected finding during urgent surgery performed for re-bleeding. One of the perforations was noted to be 0.5 cm from the site of heater probe therapy and the other at the site of therapy. Five other adverse events occurred in the thrombin group; two patients sustained myocardial infarction with a background of known ischaemic heart disease. Three of the four patients from the placebo group who developed cardiovascular adverse events had risk factors including previous stroke, ischaemic heart disease and diabetes.

Table 3.3 Outcome of treatment in relation to major stigmata

	Heater probe plus thrombin		Heater probe plus placebo	
	Active bleeding	Non-bleeding visible vessel	Active bleeding	Non-bleeding visible vessel
n	49	78	45	75
Primary haemostasis (%)	46 (94)	77 (99)	42 (93)	74 (99)
Re-bleed (%)	8 (17)	11 (14)	5 (12)	12 (16)
Emergency surgery (%)	9 (18)	7 (9)	5 (11)	8 (11)
30-day mortality (%)	3 (6)	5 (6)	7 (16)	7 (9)
Permanent haemostasis (%)	38 (78)	66 (85)	37 (82)	62 (83)
Median units transfused (range)	3 (0-22)	3 (0-32)	3 (0-22)	2 (0-35)
Total units transfused	204	266	184	249
Median duration of admission (range), days	6 (2-54)	5 (2-82)	6 (2-121)	5 (1-80)

Table 3.4 Adverse events

	Thrombin	Placebo
Myocardial infarction	2	1
Pulmonary embolus	0	1
Stroke	2	2
Deep venous thrombosis	1	0
Visceral Perforation	3	0

Eight patients (6%) in the thrombin group died within 30-days compared to fourteen patients (12%) in the placebo group ($\chi^2_c = 1.6$, $p = 0.21$). In patients treated with thrombin the relative risk of death was 0.54 (95% CI, 0.23-1.24) compared with those receiving placebo. The reduction in absolute risk of death was 5.4% (95% CI, – 12.5% - 1.8%) in patients receiving thrombin. Primary haemostasis had failed in three of these twenty-two patients, and a further eleven had re-bled. Nine patients had had an emergency operation; three for failed haemostasis and the remainder for re-bleeding. The majority of deaths occurred from decompensation of co-morbid disease, particularly in those patients who had undergone laparotomy. In one patient in each group death was due to metastatic carcinoma diagnosed after the acute bleeding episode (Table 3.5).

Table 3.5 30-day mortality

	Thrombin	Placebo
n	8	14
Exsanguination	2	6
Myocardial infarction	1	0
Congestive cardiac failure	2	1
Respiratory failure	2	2
Pulmonary embolism	0	1
Cerebrovascular accident	0	3
Metastatic carcinoma diagnosed after recruitment into trial	1	1
Median Rockall score	8	8
Median co-morbid disease score	4	5

Pre-endoscopy viral serology results were available in 245 patients. Seventy six percent of patients were antibody positive for Parvovirus B19, and 83% had antibodies to Hepatitis A. One hundred and seventy three patients agreed to undergo further blood sampling at six months post-injection. Of these, no patients had seroconverted for Parvovirus B19. One patient who had previously been negative for Hepatitis A was found to be positive. On further investigation it transpired that he had received Hepatitis A vaccine in the intervening period. No patient seroconverted for Hepatitis B or C.

Chapter 4

A randomised controlled trial comparing heater probe plus thrombin with heater probe plus placebo for bleeding peptic ulcer: Discussion

This placebo controlled, double blind trial showed that the efficacy of thrombin injection plus heater probe application was similar to that of heater probe plus placebo injection (containing albumin) in the treatment of patients admitted to hospital because of major peptic ulcer haemorrhage. Both approaches probably improved patient outcome since the overall re-bleeding rate and hospital mortality were considerably lower than would have been anticipated if no endoscopic treatment had been used (Oxner et al., 1992). It is now unethical not to apply some form of standard endoscopic therapy because the efficacy of this is undisputed. The findings of this trial are similar to those reported by Chung et al. (1997), who in an open trial showed that for the great majority of ulcer bleeding patients the haemostatic efficacy of a combination of the heater probe plus adrenaline injection was similar to that of adrenaline injection alone. In contrast to the thrombin study however these authors showed in a high-risk subgroup of actively bleeding patients that combination treatment was superior to injection treatment alone. Analysis of my results in a similar way does not suggest a benefit of combination therapy even for patients with the most severe bleeding.

In the current trial there was a trend for improved mortality in patients randomised to thrombin and a type 2 error cannot be excluded. It is noteworthy however that the re-bleeding rate, a commonly used end point in many trials which is strongly associated with death following upper gastrointestinal bleeding, was identical in both treatment groups. Furthermore other outcomes such as blood transfusion, duration of hospital admission and requirement for emergency surgery were very similar in the two groups. The need for operative surgery following failed endoscopic therapy in this

study is comparable to that reported by others (Chung et al., 1997; Choudari et al., 1992; Chung et al., 1991). These observations suggest that the small and statistically non-significant mortality difference seen in the trial should be interpreted with caution. Indeed a sample size of 700 patients would be required to confirm that this is a valid difference in mortality at the 5% level of significance with an 80% power.

In this trial, particular effort was made to remove blood clot within the ulcer base in order to accurately define and treat major stigmata. The two trials discussed in Chapter 1 have suggested this to be a safe and effective approach, although numbers included were small and pre-injection with adrenaline was performed (Bleau et al., 2002; Jensen et al., 2002). In the thrombin trial clot removal without pre-injection with adrenaline was associated with bleeding in only one of 20 patients. Spurting bleeding was produced following dislodgement of the clot. Therapy with the heater probe and thrombin injection was unable to produce primary haemostasis and a partial gastrectomy was performed. The patient survived without complication.

In this study human thrombin was chosen as the injection material. This decision was based on the theoretical considerations and clinical observations discussed in Chapter 1. The majority of clinicians inject adrenaline, which is effective but has a short duration of action. Sclerosants and alcohol produce more extensive and prolonged tissue damage, but these agents do not improve upon the results of adrenaline injection and are hazardous. Thrombin given either alone or in combination with fibrin as "fibrin glue" directly produces the desired end result of clot formation, and clinical trial evidence is promising. It was therefore believed that these 'pro-

coagulant' materials represented the injection treatments of choice in ulcer bleeding patients.

Previous clinical trials of endoscopic therapy have not included a control placebo injection. Consequently observer bias may have influenced the interpretation of some trials. In order to determine whether combinations of therapeutic modalities of proven efficacy, in this case the heater probe and thrombin injection, are superior to a single modality (the heater probe) it was considered essential to include a placebo injection and to undertake a classic double-blind randomised placebo controlled trial. The difficulty of this approach is that we cannot know with certainty that the 'placebo' injection was devoid of haemostatic activity. The trial by Lin et al. (1993) discussed in Chapter 1 demonstrated haemostatic effects of endoscopic injections of 50% dextrose, Normal saline and 3% Sodium Chloride. These were thought to be due to tamponade as the mean volume of injection was 15.9ml in the saline groups. The magnitude of the haemostatic effect of saline was questioned by the subsequent trial by Laine et al. (2002), in which a mean volume of 30ml of saline was injected. The results showed that even this very large volume of pharmacologically inactive solution was inferior to thermal endoscopic therapy.

An albumin solution was chosen as the placebo fluid in order to achieve similar protein concentrations (0.6-1.0 g/l) and viscosity in the injection fluids. There is no reason to suspect that albumin injection would influence the clotting process. The possibility that the placebo injection had a therapeutic effect in this trial cannot be excluded, but pure tamponade is unlikely to have been an important factor because

the volume of injected fluid was relatively low, and certainly much less than that used in the trial from Lin et al. (1993). It can safely be concluded therefore that thrombin was a no more effective adjunct to the heater probe than was placebo.

Adverse events were similar and infrequent in both treatment groups. In particular stroke and myocardial infarction, which might have been induced by activation of systemic coagulation following thrombin injection, were equally common in both treatment arms and developed only in patients with pre-existing atheromatous disease. The perforation rate was 1.2%, two perforations occurring in anterior duodenal ulcers and the third in a posterior duodenal ulcer. This is comparable to perforation rates reported in other series (Chung et al., 1997; Wong et al., 2002). All three perforations occurred in the thrombin group. This is most likely to be a chance finding as the numbers are small, and there are no previous reports of perforation caused by injection of thrombin or fibrin glue.

No evidence virus transmission by the thrombin or placebo injections has been demonstrated. As is the case with any blood product, there remains a theoretical risk of transmission of unknown viruses or infectious agents. In the context of major gastrointestinal bleeding most patients require a blood transfusion, and the additional risk of an injection of thrombin is likely to be insignificant.

Although all patients received proton pump inhibitor (PPI) drugs following endoscopic therapy, the use of these medications was not standardised in the trial protocol, as the evidence for their utility in reducing re-bleeding outlined in Chapter

1 was not available at the time of trial design. The majority of patients in both groups were treated with high dose oral omeprazole. Whilst it is unlikely that differences in PPI dosing between the groups had a significant effect on the results, this is a potential confounding factor.

Chapter 5

Utility of the Rockall scoring system following endoscopic therapy for bleeding peptic ulcer

No prospective studies have examined the utility of the Rockall scoring system in patients undergoing endoscopic therapy for peptic ulcer bleeding, although I have published a retrospective analysis (Church and Palmer, 2001). Since the use of endoscopic therapy is now standard clinical practice, the ability of the Rockall score to predict outcome following therapy is an important consideration, as many units triage patients to the high dependency unit or the general wards based on their Rockall scores.

The validity of a scoring system may be expressed in terms of calibration and discrimination. In this case, calibration refers to the amount of agreement between the rates of re-bleeding and mortality predicted by the score, and the observed rates in the trial patients. Discrimination concerns the ability of the score to determine which patients will re-bleed or die and which will not. Validity may also be internal or external. Internal validity evaluates a scoring system using patients recruited from the centre in which the system was derived, whereas external validation applies the system to patients from other centres. It has been shown that models perform less well when used with patients in a context outside that in which the model was developed (Lemeshow and Le Gall, 1994), and external validation is, therefore a more robust tool.

The aim of this chapter is to assess the ability of the Rockall scoring system to predict re-bleeding and death following endoscopic therapy for bleeding peptic ulcer in my trial population.

Methods

Rockall scores were calculated for all patients entered into the thrombin trial. Outcome in terms of re-bleeding, surgery and 30-day mortality was assessed according to score, and the association of these end-points with increasing score was analysed using the χ^2 test for trend.

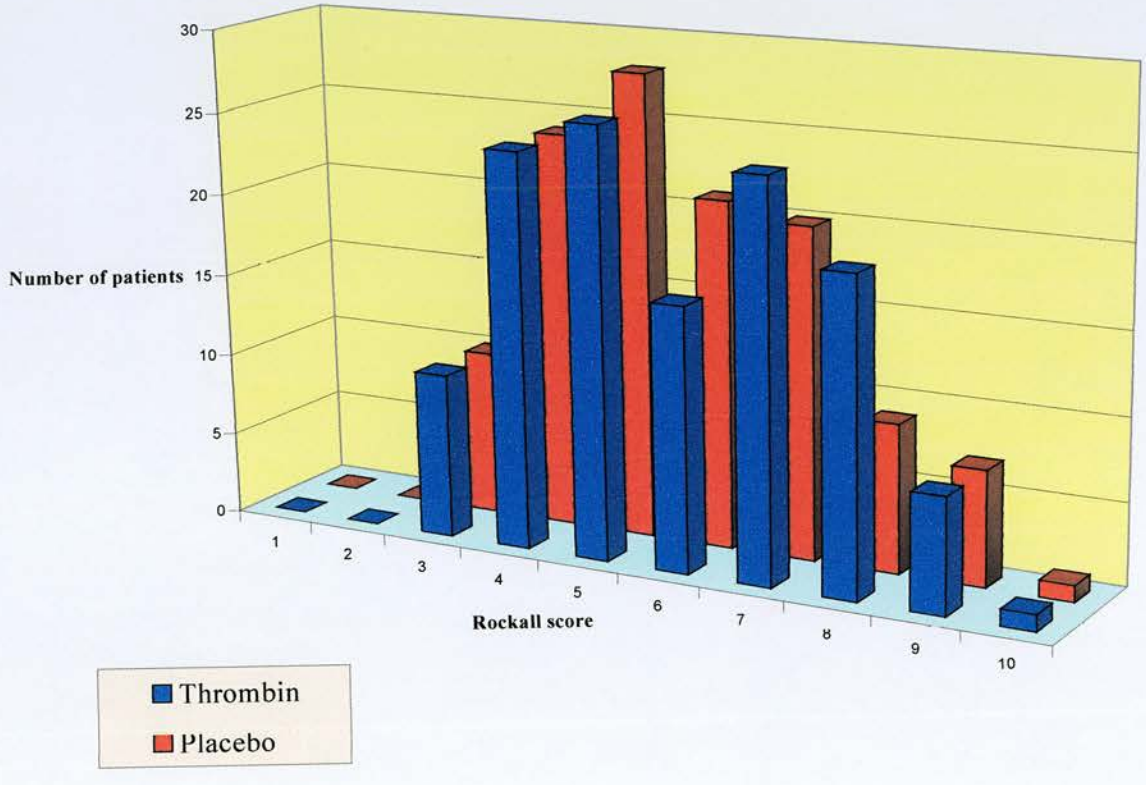
The trial patients formed a validation sample allowing the external validity of the Rockall system to be assessed. The predicted probabilities of re-bleeding and mortality were taken as the observed percentages of re-bleeding and mortality for each score category in the original patient sample in Rockall's paper (presented in table IV (B)) (Rockall et al., 1996). Calibration of the scoring system was evaluated using the Mantel-Haenszel test to compare the predicted and observed rates of re-bleeding and mortality. Receiver operating characteristic (ROC) analysis was used to assess discriminative ability. Using this method, sensitivity is plotted against 1-specificity for each cut off value of the Rockall score. For the purposes of this analysis, patients were classified as "low-risk" if they had a score below or equal to each possible cut off value and "high-risk" if their score was above this (Tables 5.2 and 5.3). The area under the resulting curve (AUC) gives a measure of the discriminative ability. An area of 50% indicates a system which is no better than

chance alone, while a perfect discriminative model would result in an AUC of 100%. Curves were plotted for both re-bleeding and mortality. Data analysis was performed using the SPSS version 10 statistical package.

Results

The Rockall scores for all 247 patients in the trial followed a fairly symmetrical distribution (Figure 5.1).

Figure 5.1 Distribution of Rockall scores



The mean score for the entire sample was 5.8. Because all patients had peptic ulcer disease with active bleeding or stigmata of recent haemorrhage, the minimum Rockall Score was three. Fifteen percent of patients re-bled within 30-days of endoscopic therapy and nine percent died. Outcome in relation to Rockall score is shown in Table 5.1. There was a significant relationship between the score and the rates of re-bleeding, need for urgent surgery and the 30-day mortality ($\chi^2_{trend} = 6.22$, $p = 0.01$ for re-bleeding; $\chi^2_{trend} = 9.69$, $p = 0.002$ for surgery; $\chi^2_{trend} = 33.3$, $p < 0.00001$ for death) (Figure 5.2).

Figure 5.2 Outcome in relation to Rockall score

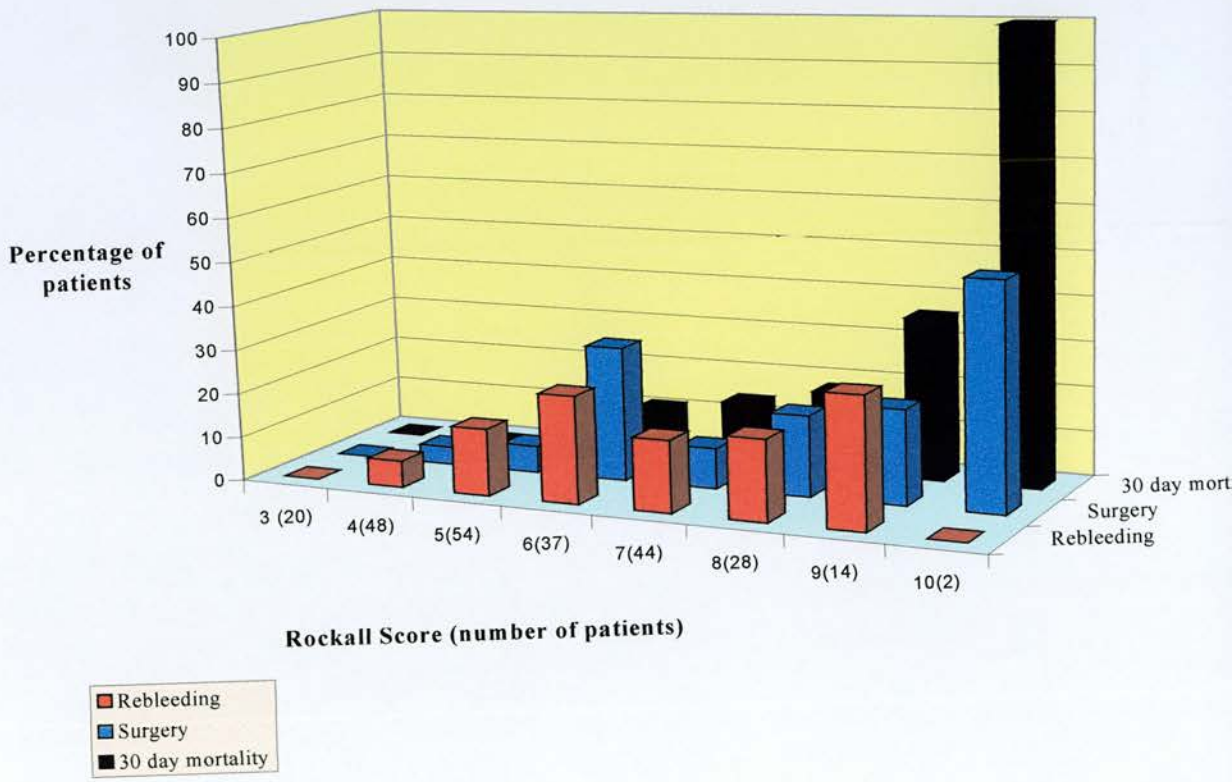


Table 5.1 Outcome in relation to Rockall score

	n	Failed haemostasis (%)	Re-bleed (%)	Surgery (%)	30-day mortality (%)
Total	247	8(3)	36(15)	29(12)	22(9)
Score 3	20	0 (0)	0 (0)	0 (0)	0 (0)
Score 4	48	2 (4)	3 (6)	2 (4)	0 (0)
Score 5	54	0 (0)	8 (15)	3 (6)	0 (0)
Score 6	37	2 (5)	9 (24)	11 (30)	4 (11)
Score 7	44	0 (0)	7 (16)	4 (9)	6 (14)
Score 8	28	3 (11)	5 (18)	5 (18)	5 (18)
Score 9	14	0 (0)	4 (29)	3 (21)	5 (36)
Score 10	2	1 (50)	0 (0)	1 (50)	2 (100)
Score 8+	44	4 (9)	9 (21)	9 (21)	12 (27)

Validation

CALIBRATION

Figure 5.3 shows the predicted probabilities of re-bleeding according to Rockall's original patient sample compared with the observed percentages in the validation sample. The predicted probabilities were higher than the observed re-bleeding rates

in all risk categories, particularly for the higher score groups. There was strong evidence that predicted and observed re-bleed rates were different (Mantel-Haenszel test, $\chi^2 = 25.8$, $p < 0.0001$).

Figure 5.3 Expected versus observed re-bleeding by risk score

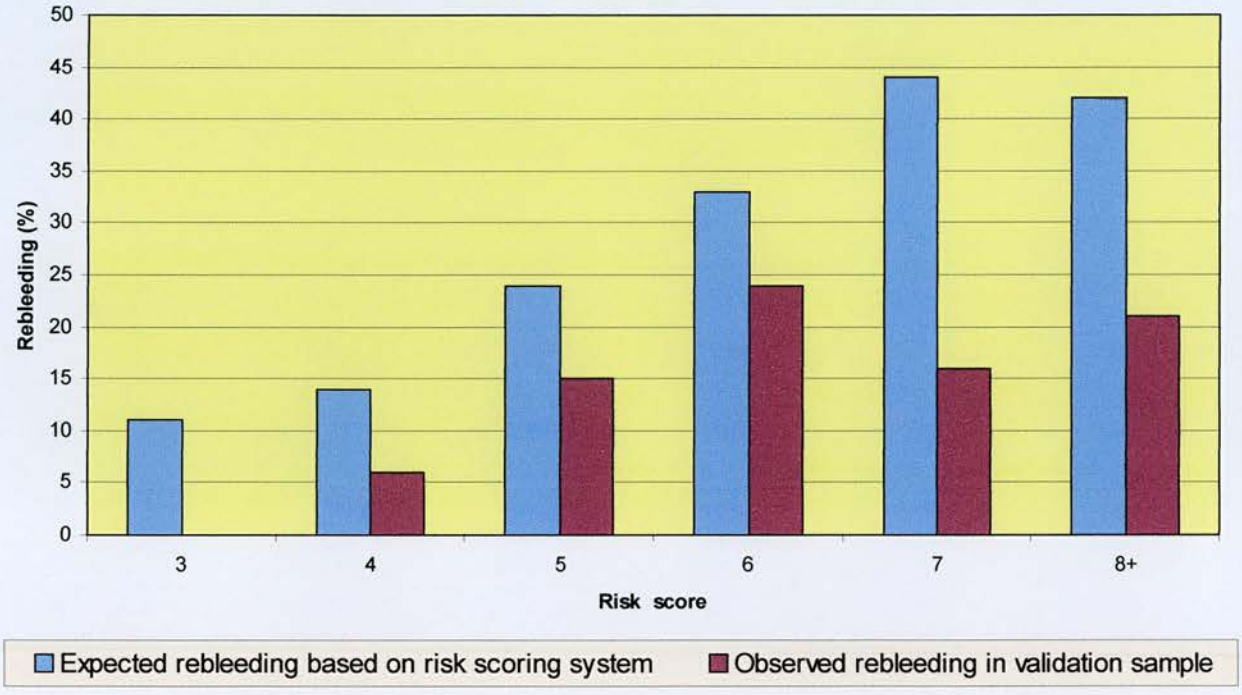
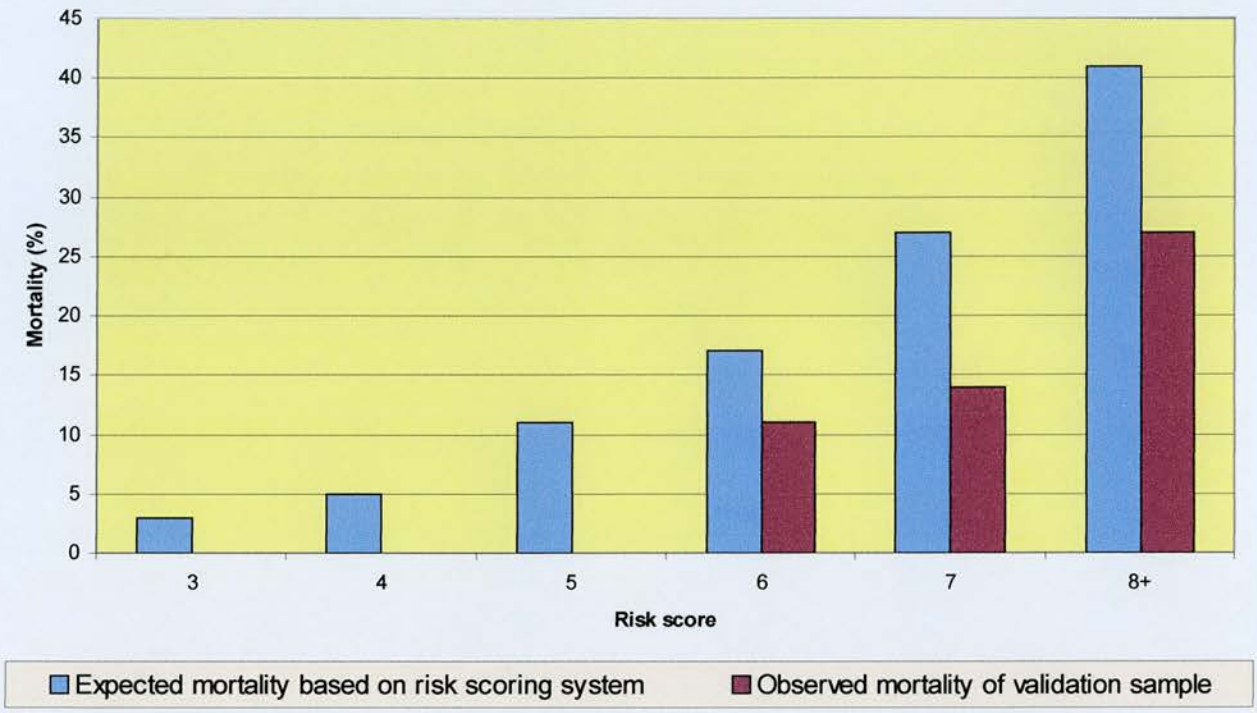


Figure 5.4 shows the predicted mortality compared with the observed mortality rates. Again the observed rates were lower than the predicted mortality, and the differences were significant (Mantel-Haenszel test, $\chi^2 = 15.1$, $p < 0.0001$).

Figure 5.4 Expected versus observed mortality by risk score



DISCRIMINATION

Sensitivity and specificity for re-bleed

The Rockall score ranged from 3 to 10. The best balance between high sensitivity and high specificity occurred when patients with Rockall scores of three to five were considered "low-risk" and patients with higher scores were considered to be "high-risk". The sensitivity and specificity achieved at this cut-off value were 69% and 53% respectively (Table 5.2). The ROC curve based on different cut-off values for Rockall's score is given in Figure 5.5. The area under the curve is 63.4%. The area

under the curve is not particularly high, and the sensitivity and specificity are not particularly high when the best cut-off is chosen.

Sensitivity and specificity for death

The Rockall score ranged from 3 to 10. The best balance between high sensitivity and high specificity occurred when patients with Rockall scores of three to six were considered "low-risk" and patients with higher scores were considered to be "high-risk". The sensitivity and specificity achieved at this cut-off were 82% and 69% respectively (Table 5.3). The ROC curve based on different cut-off values for Rockall's score is given in Figure 5.6. The area under the curve is 84.3%.

Table 5.2 Rockall score applied to observed re-bleed

Score (low-risk / high-risk)	Patients in high-risk group		Sensitivity	Specificity	Positive predictive value	Negative predictive value
	Total (n = 247)	Who had a re-bleed (n = 36)				
3 / 4-10	227	36	100.0	9.5	15.9	100.0
3-4 / 5-10	179	33	91.7	30.8	18.4	95.6
3-5 / 6-10	125	25	69.4	52.6	20.0	91.0
3-6 / 7-10	88	16	44.4	65.9	18.2	87.4
3-7 / 8-10	44	9	25.0	83.4	20.5	86.7
3-8 / 9-10	16	4	11.1	94.3	25.0	86.1
3-9 / 10	2	0	0.0	99.1	0.0	85.3

Figure 5.5 Receiver Operating Characteristic Curve for Rockall score applied to observed re-bleed

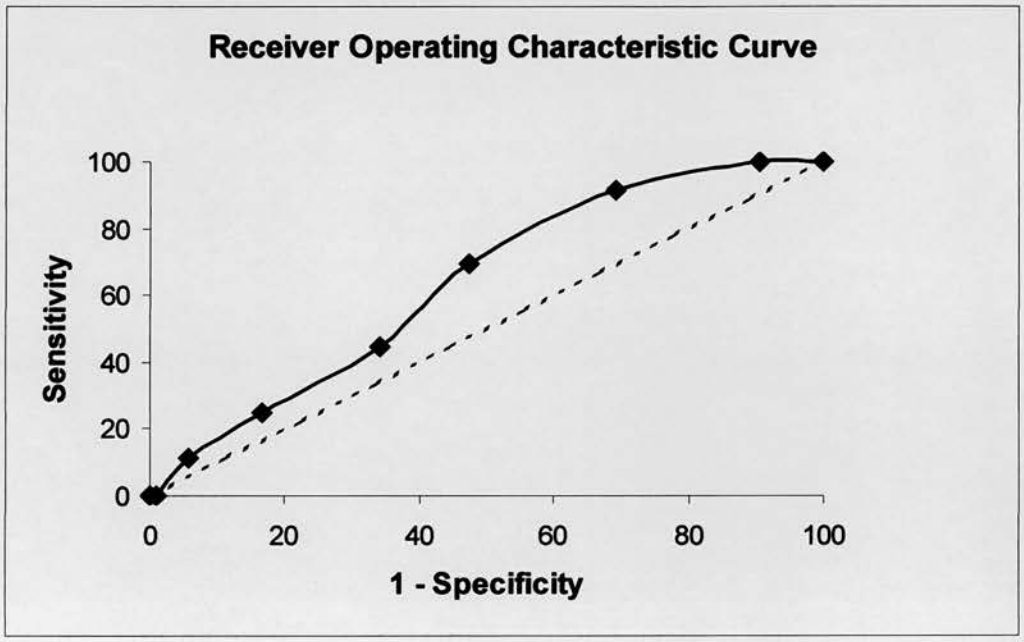
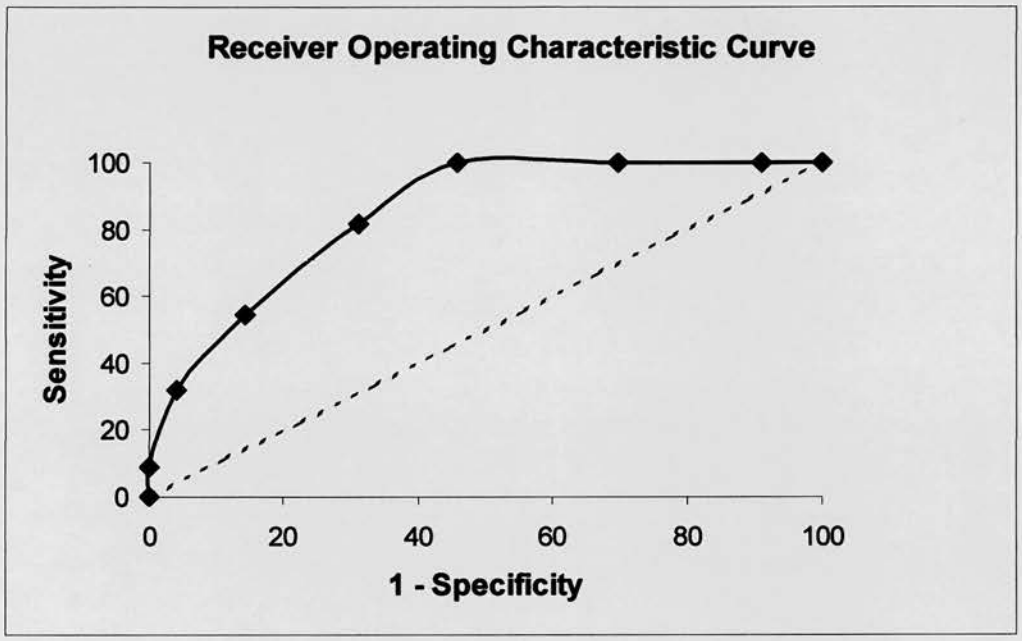


Table 5.3 Rockall score applied to observed mortality

Score (low-risk / high-risk)	Patients in high-risk group		Sensitivity	Specificity	Positive predictive value	Negative predictive value
	Total (n = 247)	Who died (n = 22)				
3 / 4-10	227	22	100.0	8.9	9.7	100.0
3-4 / 5-10	179	22	100.0	30.2	12.3	100.0
3-5 / 6-10	125	22	100.0	54.2	17.6	100.0
3-6 / 7-10	88	18	81.8	68.9	20.5	97.5
3-7 / 8-10	44	12	54.5	85.8	27.3	95.1
3-8 / 9-10	16	7	31.8	96.0	43.8	93.5
3-9 / 10	2	2	9.1	100.0	100.0	91.8

Figure 5.6 Receiver Operating Characteristic Curve for Rockall score applied to observed mortality



Discussion

The Rockall score (Rockall et al., 1996) was developed in 1996 and has been widely adopted in clinical practice. The scoring system was developed from an analysis of data obtained from a large audit of patients presenting with upper gastrointestinal bleeding due to a wide range of causes and only a minority of patients received endoscopic therapy. The current analysis was designed to determine whether the Rockall system is applicable to the subset of high-risk ulcer bleeding patients who receive endoscopic haemostatic therapy. It was also desirable to identify a cut off point below which patients could be deemed to be at low-risk of poor outcome. This is an important area because the score has been used to define prognosis, and in particular to aid decision making in relation to patient placement in high dependency units or the general ward.

The results of this analysis show that after endoscopic therapy higher Rockall scores correlate significantly with re-bleeding, requirement for surgery and 30-day mortality. The calibration of the system is poor, however, with significant differences between the rates of predicted and observed re-bleeding and mortality. This is not surprising since the two patient groups were not matched and there are thus differences between the groups, particularly in terms of the severity and type of bleeding, and the percentage of patients receiving endoscopic therapy. Although the absolute percentages differ in the predicted and observed groups, the patterns of both re-bleeding and mortality are similar, the rates rising with increasing score.

Of greater clinical significance is the discriminative ability of the scoring system. This is poor when considering re-bleeding (AUC 63.4%) and meaningful recommendations regarding patient management cannot therefore be made on the basis of the Rockall score. In the case of mortality the discriminative ability is much better (AUC 84.3%), and at the cut off value of six (patients scoring six or less "low-risk", score of seven and above "high-risk"), sensitivity and specificity for prediction of death are adequate. When considering cut off values, however, it is important to interpret the clinical significance of the different outcomes, and the positive and negative predictive values of a model become more important. In this case the clinical significance of the end-point (death) is high. It is therefore most important to accurately predict that a patient will not die in order to triage them to a general ward rather than to a high dependency unit following endoscopy. A more sensible cut off point would then be a score of five because no patient scoring five or less died, resulting in a negative predictive value of 100% (See Table 5.3). From this data it could be recommended that patients with a Rockall score of six or greater should be managed in a high dependency area, while those with lower scores could be transferred to a general ward. There would be considerable resource implications in the implementation of such a policy, and to confirm this recommendation, a randomised trial to assess outcome in terms of post endoscopy placement would be required.

The Rockall scoring system has been externally validated in a Dutch population by Vreeburg et al. (1999). This study included similar patients to those used by Rockall in the development of the score. All patients presenting with symptoms and/or signs

or upper gastrointestinal bleeding were included, Rockall scores were calculated and re-bleeding and mortality rates observed. These rates were then compared with predicted re-bleeding and mortality rates from Rockall's paper. The patients in Vreeburg's study were thus different to the patients in the thrombin trial, the latter being restricted to high-risk patients bleeding from peptic ulcer in whom endoscopic therapy had been applied. Despite these differences the validation results obtained in this analysis are similar to those of Vreeburg's group. Vreeburg et al. found the Rockall system to be poorly calibrated. In the lower score groups the predicted re-bleeding rate was lower than the observed rate, while in the high score groups the converse was true. These differences were significant ($p<0.0001$ by χ^2 goodness of fit). Mortality rose with increasing score in both predicted and observed groups and the differences between them were not statistically significant ($p=0.2$ by χ^2 goodness of fit). The discriminative ability of the Rockall system was poor for the prediction of re-bleeding (AUC 61%), but for mortality the AUC was 73% suggesting the main role of the system to be the prediction of mortality. The results of my analysis closely mirror Vreeburg's results and show that although the calibration of the scoring system may be changed following endoscopic therapy in high-risk ulcer bleeding patients, the discriminative ability remains good for the prediction of mortality and poor for the prediction of re-bleeding.

On first inspection the Rockall scoring system appears complicated. Despite this, calculation of Rockall scores is straightforward, and the required information is readily obtainable from patient records or trial databases. Co-morbid disease in the trial patients was recorded in a different way to the classification of co-morbidity

used by Rockall (see Chapter 2), but the detailed documentation of co-morbid conditions in our patients allowed accurate calculation of the Rockall score.

In conclusion, re-bleeding and mortality rates correlate with Rockall scores in patients undergoing endoscopic therapy for bleeding peptic ulcer. Patients with scores of six or greater have a significantly poorer outcome. Calculation of a Rockall score may be a clinically useful way to predict which patients will do badly, facilitating decisions concerning post-endoscopy placement and monitoring.

Chapter 6

The impact of co-morbid disease upon outcome

Introduction

Co-morbid illness greatly influences outcome from peptic ulcer bleeding and the majority of deaths occur in patients with significant co-morbidity. This was particularly evident in the papers produced by Rockall et al. (Rockall et al., 1995; Rockall et al., 1995; Rockall et al., 1996; Rockall et al., 1996). The presence of co-morbid illness has also been reported to influence the success of endoscopic therapy (Villanueva et al., 1993). In the study reported in this thesis, the severity of co-morbid disease was carefully defined and scored as described in Chapter 2. In this chapter the impact of co-morbid disease on outcome of the trial patients is analysed.

Method

The different co-morbid conditions were scored on a scale from 0-3 where 0 represents no disease, 1 represents mild disease, 2 represents moderate disease and 3 represents severe disease (see Table 2.1). The total score for each patient in the trial was calculated and patients were separated into score groups. Outcome following endoscopic therapy was related to total score. Because the number of patients with scores greater than six was small, patients scoring six or above were also considered as one group. Rates of re-bleeding, surgery and 30-day mortality in each score group were compared using the χ^2 test for trend.

In order to assess the individual contribution of each co-morbid condition to overall outcome, logistic regression models were produced for each of the three major end-

points of re-bleeding, surgery and 30-day mortality. Due to the small number of patients in certain categories the co-morbidity variables were re-coded and analysed as "no disease" and "mild disease" combined (representing minor co-morbidity) compared with "moderate disease" and "severe disease" combined (indicating the presence of significant co-morbid disease). The stepwise procedure was used with variables entering and leaving the models at the 5% significance level. Independent predictors of re-bleeding, surgery and 30-day mortality were determined using the Wald χ^2 test and are presented as odds ratios with 95% confidence intervals. Data analysis was performed using the SPSS version 10 statistical package.

Results

The majority of patients had low total co-morbidity scores as shown in Figure 6.1.

The number of patients with disease in each category is shown in Table 6.1. Cardiovascular disease was the most prevalent co-morbid condition, followed by arthritis, respiratory and neurological diseases. The other categories were represented to a lesser extent. Moderate or severe disease was predominantly cardiorespiratory in nature.

Figure 6.1 Distribution of co-morbid disease scores

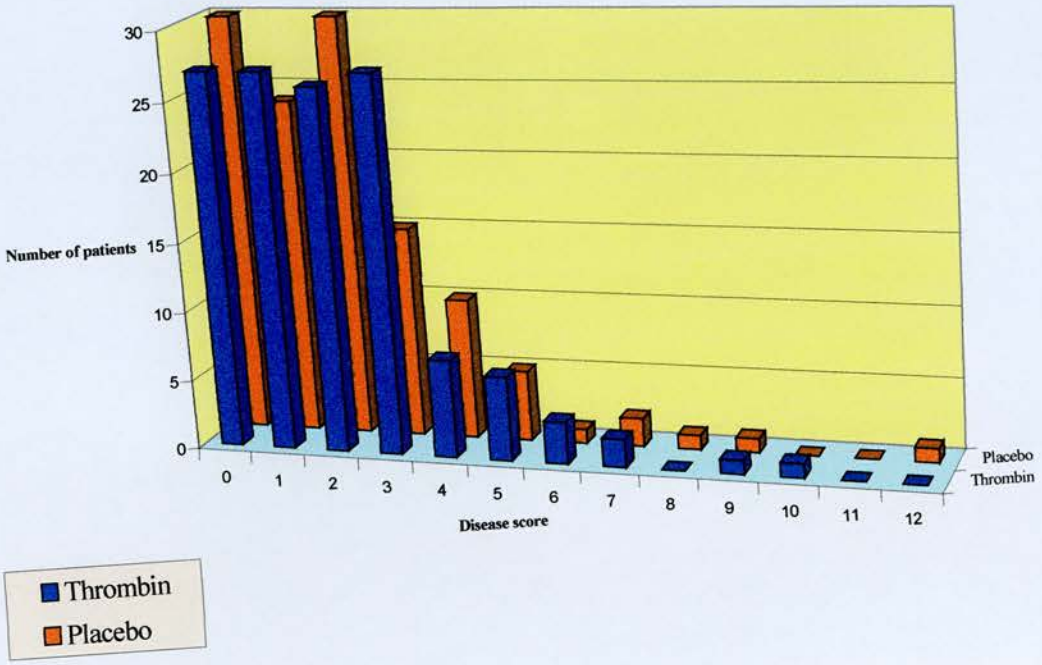


Table 6.1 Number of patients with disease by category

Category	Number of patients with any severity of disease (%)	Number of patients with moderate or severe disease (%)
Liver/GI	11 (5)	0 (0)
Heart/Vascular	122 (49)	39 (16)
Chest	48 (19)	24 (10)
Diabetes	19 (8)	2 (1)
Arthritis	70 (28)	8 (3)
Stroke/Neurology	48 (19)	15 (6)
Renal	19 (8)	5 (2)
Cancer	19 (8)	13 (5)
Operation/Trauma	10 (4)	5 (2)

OUTCOME ACCORDING TO DISEASE SCORE

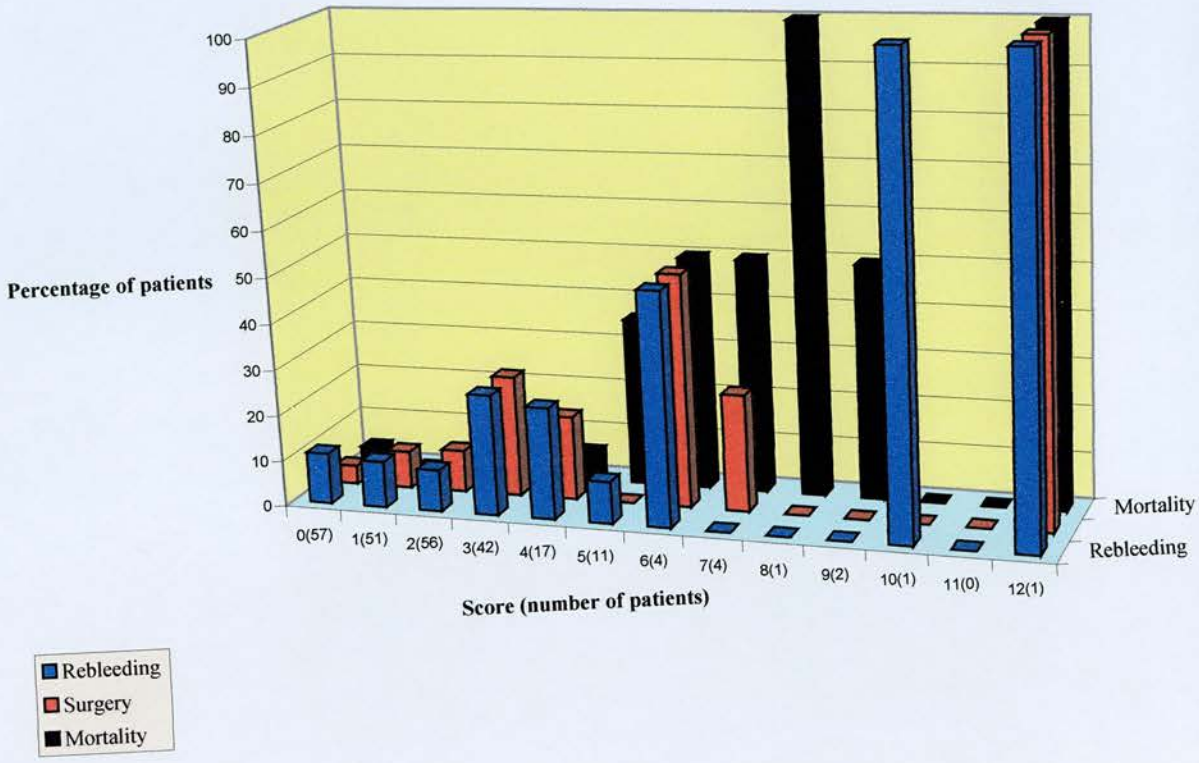
The outcome in relation to the co-morbid disease score is shown in table 6.2. There was a close relationship between increasing co-morbid disease score and rates of re-bleeding, surgery and 30-day mortality ($\chi^2_{trend} = 6.817$, $p = 0.009$ for re-bleeding, $\chi^2_{trend} = 9.086$, $p = 0.003$ for surgery, $\chi^2_{trend} = 38.44$, $p < 0.0001$ for mortality) (Figure 6.2).

Table 6.2 Outcome in relation to co-morbid disease score (1)

	n	Re-bleed (%)	Surgery (%)	30-day mortality (%)
Total	247	36 (15)	29 (12)	22 (9)
Score 0	57	6 (11)	2 (4)	2 (4)
Score 1	51	5 (10)	4 (8)	0 (0)
Score 2	56	5 (9)	5 (9)	3 (5)
Score 3	42	11 (26)	11 (26)	5 (12)
Score 4	17	4 (24)	3 (18)	1 (6)
Score 5	11	1 (9)	0 (0)	4 (36)
Score 6	4	2 (50)	2 (50)	2 (50)
Score 7	4	0 (0)	1 (25)	2 (50)
Score 8	1	0 (0)	0 (0)	1 (100)
Score 9	2	0 (0)	0 (0)	1 (50)
Score 10	1	1 (100)	0 (0)	0 (0)
Score 11	0	0 (0)	0 (0)	0 (0)
Score 12	1	1 (100)	1 (100)	1 (100)
p *	-	0.009	0.003	<0.0001

* χ^2_{trend}

Figure 6.2 Outcome in relation to co-morbid disease score (1)



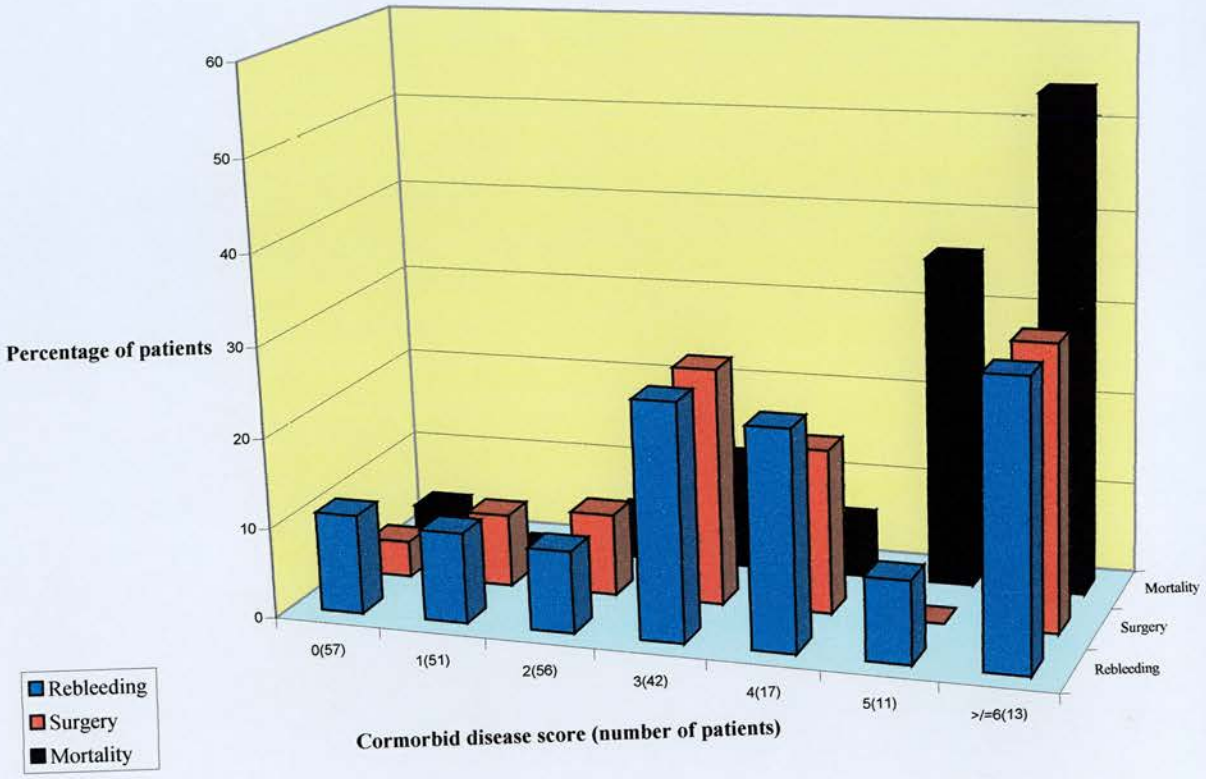
When patients with scores of six or above were considered as one group the results were similar ($\chi^2_{trend} = 5.376$, $p = 0.02$ for re-bleeding, $\chi^2_{trend} = 8.995$, $p = 0.003$ for surgery, $\chi^2_{trend} = 33.29$, $p < 0.0001$ for mortality) (Table 6.3, Figure 6.3).

Table 6.3 Outcome in relation to co-morbid disease score (2)

	n	Re-bleed (%)	Surgery (%)	30-day mortality (%)
Total	247	36 (15)	29 (12)	22 (9)
Score 0	57	6 (11)	2 (4)	2 (4)
Score 1	51	5 (10)	4 (8)	0 (0)
Score 2	56	5 (9)	5 (9)	3 (5)
Score 3	42	11 (26)	11 (26)	5 (12)
Score 4	17	4 (24)	3 (18)	1 (6)
Score 5	11	1 (9)	0 (0)	4 (36)
Score 6 or greater	13	4 (31)	4 (31)	7 (54)
p *	-	0.02	0.003	<0.0001

* χ^2_{trend}

Figure 6.3 Outcome in relation to co-morbid disease score (2)



EFFECT OF DIFFERENT CO-MORBID CONDITIONS

Re-bleeding

When 'no disease' was combined with 'mild disease' and compared with 'moderate disease' and 'severe disease' combined then neurological disease was the only co-morbidity which predicted re-bleed when each co-morbidity was considered separately (χ^2 test with continuity correction 7.1, $p = 0.008$). The odds ratio of re-bleed was four for moderate/severe cases compared to those who had only mild disease. In

stepwise logistic regression, neurology and cancer were significant independent predictors of re-bleeding (Table 6.4).

Table 6.4 Significant independent predictors of re-bleed

Co-morbidity	Moderate/severe disease compared to none/mild disease		
	Wald χ^2	p	OR (95% CI)
Neurological	8.75	0.003	5.11 (1.73, 15.1)
Cancer	4.64	0.031	3.65 (1.12, 11.9)

Surgery

When 'no disease' was combined with 'mild disease' and compared with 'moderate disease' and 'severe disease' combined, then neurological disease was associated with surgery (χ^2 test with continuity correction 5.1, $p = 0.023$) with an odds ratio of four for moderate/severe cases compared to those who had no disease or mild disease (OR 4.33, 95% CI 1.37, 13.7). In stepwise logistic regression, neurological and respiratory diseases were significant independent predictors of surgery (Table 6.5).

Table 6.5 Significant independent predictors of surgery

Co-morbidity	Moderate/severe disease compared to none/mild disease		
	Wald χ^2	p	OR (95% CI)
Neurological	6.70	0.010	4.71 (1.46, 15.2)
Respiratory	4.67	0.031	3.15 (1.11, 8.91)

30-day mortality

When 'no disease' was combined with 'mild disease' and compared with 'moderate disease' and 'severe disease' combined then those with moderate or severe respiratory disease (χ^2 test with continuity correction 6.1, p = 0.014, OR 3.58, 95% CI 1.39, 9.23), heart disease (χ^2 test with continuity correction 23.0, p < 0.001, OR 9.69, 95% CI 3.57, 26.3), and neurological disease (χ^2 test with continuity correction 15.2, p < 0.001 OR 9.00, 95% CI 2.85, 28.5) had increased odds of 30-day mortality compared to those without the diseases/conditions. In stepwise logistic regression, respiratory, neurological and renal diseases were significant independent predictors of 30-day mortality (Table 6.6).

Table 6.6 Significant independent predictors of 30-day mortality

Co-morbidity	Moderate/severe disease compared to none/mild disease		
	Wald χ^2	p	OR (95% CI)
Respiratory	21.3	<0.001	14.5 (4.65, 44.9)
Neurological	18.1	<0.001	16.9 (4.60, 62.0)
Renal	5.18	0.023	11.8 (1.41, 99.0)

The co-morbid disease score used in this study includes disease of all major organ systems, recent surgery and trauma. Although an arbitrary score is allocated to the severity of disease within each system, the complete score is a comprehensive index of a patient's state of health rather than a simple grading of co-morbidity into "minor" or "major" categories.

This analysis suggests that poor outcome following endoscopic therapy for major upper gastrointestinal bleeding is correlated with the extent of a patient's co-morbid disease. The previously published risk scoring systems discussed in Chapter 1 (Rockall et al., 1996; Saeed et al., 1993; Pimpl et al., 1987; Garripoli et al., 2000; Guglielmi et al., 2002) universally include co-morbid disease as a major component, supporting its importance as a predictor of poor outcome. Logistic regression analysis demonstrates that significant neurological conditions and malignancy are independent predictors of re-bleeding. Similarly, neurological and respiratory co-morbidity is associated with requirement for surgery and the presence of neurological, respiratory and renal disease is predictive of 30-day mortality.

In the published papers (Rockall et al., 1996; Saeed et al., 1993; Pimpl et al., 1987; Garripoli et al., 2000; Guglielmi et al., 2002), cardiac failure, ischaemic heart disease, renal failure, liver failure and malignancy are the most significant co-morbid conditions affecting outcome. In this study, significant liver disease and widespread

malignancy were excluded, but patients with mild liver disease and localised or treated cancer were included.

In this patient group, neurological disease appears to be the most important co-morbid condition, affecting re-bleeding, surgery and mortality. The majority of patients in this trial with significant neurological co-morbidity had suffered a recent or acute stroke. It is unlikely that stroke per se would predispose to failure of endoscopic therapy, although nutritional deficiencies resulting in poor wound healing could be implicated. A more plausible explanation is that stroke is a marker of more generalised vascular disease. There is a strong association between cerebrovascular disease and vascular disease elsewhere, one study showing that 35% of patients with symptomatic cerebrovascular or carotid artery disease also had severe coronary artery disease which was often asymptomatic (Graor et al., 1998). Generalised vascular changes in our trial patients could have affected the responsiveness of involved blood vessels to endoscopic therapy. If should be noted, however, that pathological specimens of resected ulcers do not demonstrate significant atherosclerotic changes in the bleeding vessels (Swain et al., 1986) (see Chapter 1). A number of other important factors could have resulted in an increased mortality in these patients. Stroke results in cardiac complications which are not due to underlying coronary artery disease. These include repolarization and ECG abnormalities (Goldstein, 1979), cardiac arrhythmias (Rem et al., 1995) and neurogenic cardiac damage (Oppenheimer and Norris, 1995). In addition, respiratory complications are common following stroke and include aspiration pneumonia, abnormal respiratory patterns and more rarely neurogenic pulmonary oedema.

Respiratory conditions confer a high-risk of poor outcome probably due to reduced tolerance of sedation and general anaesthesia with resultant tissue and end-organ hypoxia.

The presence of localised or treated cancer was predictive of re-bleeding but not mortality. This is likely to be due to the fact that patients with widespread malignancy were not included in the trial. Malignancy may be associated with re-bleeding due to nutritional deficiencies resulting in impaired tissue healing. In addition, many tumours have been shown to be associated with impaired coagulation due to acquired inhibitors of factor VIII (Sallah and Wan, 2001) factor V (Knobl and Lechner, 1998), although levels of these factors were not measured in my patients.

Renal failure is associated with poor tissue healing, generalised vascular disease, cardiac failure, and multiple other reasons for poor outcome. It is, therefore, not surprising that this condition is an independent predictor of mortality.

The fact that cardiovascular co-morbidity was not independently associated with re-bleeding or requirement for surgery might suggest that generalised vascular disease does not play a major role in failure of endoscopic therapy. The lack of association of cardiovascular disease with mortality was unexpected. The sample contained enough patients with cardiovascular disease to make valid comment, but of the 122 patients with cardiovascular disease, 83 had disease in the "mild" category. It is possible that the result would have been different had more patients with moderate or severe cardiovascular morbidity been included.

Further studies would be required to define the individual importance of the different co-morbid conditions contributing to the overall disease score used in this trial. This could allow for "weighting," with more important conditions contributing greater numbers to the overall score than those with lesser influence. In its present form the score appears to be clinically useful, with rising scores correlating with increased rates of re-bleeding, surgery and mortality. It would be desirable to prospectively validate the score in an independent group of patients. In studies of endoscopic therapy for GI bleeding, differences in end points are small. It is therefore important to restrict entry into trials of endoscopic therapy to only those patients at highest risk for failure of therapy. It is also important to ensure that groups within trials are as closely matched as possible, and that results of trials in different populations can be compared. With further refinement, this co-morbid disease score could be used in conjunction with clinical parameters to facilitate both these goals.

Chapter 7

Use of the heater probe for bleeding peptic ulcer – effect of heater probe diameter

The heater probe (Olympus HPU, Olympus Corporation, Melville, NY) is a contact thermal device which is inserted down the biopsy channel of an endoscope. The probe is 3m long and is produced in 2.4mm and 3.2mm diameters. The probe tip consists of a rigid section 15mm long with 3 irrigation nozzles at the proximal end, allowing irrigation in an umbrella fashion at a series of preset levels controlled by a foot switch. The distal end of the tip consists of a brass cylinder with a rounded end. This contains an avalanche diode which is heated when the foot switch is depressed. The diode enables rapid heating to a defined temperature and then switches off the current when a preset amount of energy has been delivered. Initial versions of the probe heated the tip to 150 ^{o}C while the current version heats to 250 ^{o}C. The temperature at the tip is maintained until 5-30 joules have been delivered. The probe delivers 30 J in 8-10 seconds in air, this falling to 3-5 seconds when immersed in water. In order to minimise adherence to treated tissue the tip is Teflon coated. A standard therapeutic technique has been adopted for treatment of peptic ulcers with active bleeding or non-bleeding visible vessels (Johnston et al., 1985). The probe is used to firmly tamponade the bleeding point and is then activated at the 20-30 J setting. Two to three applications are applied before moving the probe and reapplying therapy. Treatment is continued until bleeding has ceased and the bleeding point is blackened and cavitated.

EXPERIMENTAL USE OF THE HEATER PROBE

Use of the heater probe was first reported by Protell et al. (1978). The probe was used to treat experimental ulcer bleeding and the 3.2mm probe stopped bleeding in 18 of 19 ulcers. Further experimental work involved an experimental model of acute peptic ulceration using canine mesenteric arteries. In 1984 Johnston et al. reported a trial which compared the effects of laser, monopolar and bipolar electrocoagulation (BICAP), electrofulguration and heater probe on experimental arterial bleeding. The most effective approach was that of coaptive coagulation, in which the bleeding vessel is first compressed before heat is applied. The heater probe and the bipolar probe were found to be equivalent and superior to the other methods, and had a lesser degree of undesirable tissue erosion. This was followed up with a trial comparing the heater probe with the BICAP (Johnston et al., 1985). The two modalities were found to be similar, but bond strength with the heater probe was greater than that for the BICAP (1459 vs 765 mmHg), and the heater probe was associated with a lesser degree of tissue adherence. These results are supported by those of Swain et al. (1984) in a similar study. Two experimental studies assessed the efficacy of probes of different sizes. Morris et al. (1985) compared the effects of the 2.3mm and 3.2mm BICAP probes on canine arteries. The 3.2mm probe was more effective for vessels which were 1.2mm in diameter or larger. A study by Jensen et al. (1982) concluded that the 2.4mm and 3.2mm heater probes were similar in efficacy.

CLINICAL TRIALS

The important clinical trials involving the heater probe are discussed in Chapter 1. The trial by Matthewson et al. (1990) is the only clinical trial to include an assessment of the outcome according to size of heater probe used. One hundred and forty three patients were randomised to one of Nd-YAG laser, heater probe or conservative therapy. During this trial the randomisation proportions were altered to three heater probe: one laser: one control, in order to increase the power of the comparisons between heater probe and control, and heater probe and laser. While the laser treated patients had a significantly lower re-bleeding rate than the control group (20% versus 43%), a significant advantage was not demonstrated for the heater probe group (Table 1.12). Of the 57 patients randomised to the heater probe, 42 were treated with the 3.2mm probe. In the remaining 15 patients the 2.4mm probe was used due to lack of availability of an endoscope with a large biopsy channel. Re-bleed rates in the large and small probe groups were 24% and 40% respectively. These were not significantly different from the control group (43%) but demonstrated a trend in favour of the large diameter probe.

RATIONALE

Experimental studies using canine models have suggested that thermal endoscopic haemostatic methods are only effective in arteries up to 2mm in diameter (Swain et al., 1984; Michaeletz and Judge, 1989; Johnston et al., 1987). Studies on post-operative resection specimens reveal that the majority of ulcer bleeding arises from

vessels with a diameter of less than 2mm (Swain et al., 1986), but when post-mortem ulcers are examined, vessels up to a diameter of 3.45mm have been reported (Lai and Swain, 1993). It is logical to propose that the large heater probe should be more effective than the small probe, and it has been stated that the 3.2mm probe is required for optimum effect (Chung et al., 1997). There is experimental support for this view (Morris et al., 1985), but a lack of clinical trial evidence. This analysis aims to further define the outcome of endoscopic therapy according to size of heater probe used.

Method

The trial reported in this thesis shows that the combination of heater probe with human thrombin injection is no better than the combination of heater probe with placebo injection. In this trial the majority of patients were treated with the 2.4mm probe due either to lack of availability of a large probe, or to lack of availability of a large endoscope. In order to assess the possible effect of probe diameter on outcome of treatment, the results were analysed in relation to size of probe used. The patients were divided into two groups. Group A consisted of those patients treated with the 2.4mm probe, while the remainder were designated as group B.

Statistical analysis

Baseline characteristics of the study groups were compared using the Mann-Whitney test for continuous variables, and the χ^2 test with Yates' correction for categorical

variables. Differences in proportions for the study outcomes were analysed using the χ^2 test with Yates' correction, and were considered significant at a p value of less than 0.05. Data analysis was performed using the SPSS version 10 statistical package.

Results

Two hundred and sixteen patients were treated using the 2.4mm probe; the 3.2mm probe was used in the remaining 31 patients. No technical problems were encountered when using the large channel endoscope, and all lesions were accessible to treatment. Table 7.1 shows the characteristics of the two groups. Group A contained a small number of patients with oesophageal ulcers and fewer patients in this group received thrombin as the injection material. A greater number of patients in group A had suffered a bleed while in hospital. None of these differences were significant. The groups were well matched for the other factors associated with severity of a bleeding episode, specifically the presence of shock, co-morbid disease severity, ulcer size, presence of duodenal ulcer and active bleeding. The only statistically significant difference between the groups was in the volume of injection used.

Table 7.2 shows the outcome according to probe size. Haemostasis failed in eight patients in group A. Five of these presented with actively bleeding ulcers. In the remaining three patients endoscopic therapy induced torrential bleeding which could not be controlled. Emergency surgery was carried out in six of the eight patients and three had died within 30-days. Primary haemostasis was successful in all patients in

the group B. There was a trend towards a reduction in re-bleed rate in group A but this did not achieve statistical significance ($\chi^2_c = 1.164$, $p = 0.28$). Similarly, there was a non-significant trend towards reduction in surgery in the small probe group. Mortality rates were equivalent in the two groups.

Adverse event rates were similar in the groups (5% in group A versus 7% in group B). Three perforations occurred, all in group A. These patients all were bleeding from duodenal ulcers and had received injection with thrombin and a median of 120 J of therapy with the 2.4mm probe. One perforation was thought to have been present prior to endoscopic therapy.

Table 7.1 Characteristics of patients treated with small and large heater probe

	Small probe	Large probe	p
n	216	31	-
Median age (range)	72 (20-94)	75 (34-92)	0.92
Shock (%)	137 (63)	19 (61)	0.96
Median (range) haemoglobin (g/dl)	9.3 (6.2-18.1)	9.65 (4.0-14.4)	0.66
Median co-morbid disease score (Range)	2 (0-12)	2 (0-7)	0.90
Median Rockall score (Range)	5.5 (3-10)	6 (3-8)	0.97
Median (range) ulcer size (mm)	10 (1-50)	10 (3-50)	0.33
GU (%)	72 (33)	14 (47)	0.49
DU (%)	127 (59)	16 (52)	0.81
Oesophageal (%)	9 (4)	0 (0)	0.54
Stomal (%)	8 (4)	1 (3)	0.70
Spurting (%)	11 (5)	1 (3)	1.00
Oozing (%)	70 (32)	11 (35)	0.96
Total active bleeding (%)	81 (38)	12 (39)	0.92
NBVV (%)	135 (63)	19 (61)	0.92
Median (range) HP joules	120 (30-420)	160 (80-280)	0.33
Median (range) injection volume	3.5 (2-7)	3.5 (3.5-7)	0.02
Out of hours scope (%)	66 (31)	10 (32)	0.96
In hospital bleed (%)	35 (16)	2 (7)	0.32
Thrombin (%)	108 (50)	19 (61)	0.63
Adverse events (%)	10 (5)	2 (7)	0.97
Perforation (%)	3 (1)	0 (0)	1.00

Table 7.2 Small vs large heater probe

	Small probe	Large probe	χ^2_c	p	Relative risk (95% confidence interval)
n	216	31	-	-	-
Failed haemostasis (%)	8 (4)	0 (0)	0.299	0.59	0.00 (0.00, 4.15)
Re-bleed (%)	29 (13)	7 (23)	1.164	0.28	1.68 (0.81, 3.51)
Surgery (%)	23 (11)	6 (19)	1.232	0.27	1.82 (0.80, 4.11)
30-day mortality (%)	20 (9)	2 (7)	0.031	0.86	0.70 (0.17, 2.84)

Most trials involving the heater probe have used the large probe. In order to use the large probe a specialised endoscope with a 3.7mm working channel is required. This may have a number of disadvantages. Firstly a large channel endoscope may not be available in all endoscopy units. Secondly intubation with the large channel endoscope is more difficult as compared to the standard instruments, especially in older frailer patients. Most importantly, the larger endoscope is stiffer and less manoeuvrable which may render some lesions, particularly those in the duodenal cap untreatable.

In this trial the large channel therapeutic endoscope was used in preference to a standard model when available. It was possible to intubate all patients successfully, and visualisation of the bleeding lesion was generally better due to increased capacity for clearing fresh and altered blood, and the ability to irrigate and aspirate simultaneously. All lesions were accessible to therapy despite the reduced manoeuvrability of the endoscope.

The results of this analysis suggest that in combination with an injection agent the small heater probe is as effective as the large probe. It must be acknowledged, however that the original trial was not primarily designed to determine the effect of heater probe diameter and there is a considerable disparity in the number of patients in the two arms of this analysis. This study therefore has a low power to detect differences between the treatments, should any exist, and the confidence intervals for

the relative risks presented in table 7.2 are wide. In addition, because patients were not randomised to receive therapy with either the small or the large probe, there may be important differences between the groups.

There were more oesophageal ulcers in the small probe group, but all these ulcers had active bleeding or visible vessels, and the patients had fulfilled the strict entry criteria limiting entry to the trial to those with high-risk bleeding. Had these patients not been present the results would be unchanged.

Fewer patients treated with the small probe had received thrombin injection. The overall results of the trial however, show that in combination with the heater probe, thrombin and placebo injections have similar efficacy. Thrombin was certainly not shown to have a detrimental effect on outcome, and theoretically therefore group A might have been expected to fare worse as they had not received an active therapeutic agent. A further discrepancy between the groups is the increased proportion of group A patients developing bleeding while hospitalised for another condition. This has been shown to be an independent predictor of poor outcome and should bias the results in favour of patients treated with the large probe.

Patients in group A received a slightly smaller volume of injection than those in group B. The difference in the mean volumes of injection was 0.3ml. While this difference was statistically significant it is unlikely that clinically important effects would have resulted. It has been shown that larger injection volumes tend to reduce

re-bleed rates (Lin et al., 2002) and, like the other matching differences between the groups, this would be expected to favour group B.

The trial investigators documented ulcer size but did not attempt to quantify the size of visible vessels, as accurate endoscopic assessment of size is impossible when lesions are only millimetres in diameter. It is possible that there were differences in the mean size of the vessels in the two groups, this being a further potential source of bias.

In conclusion, this analysis should be interpreted with caution due to confounding factors and low power. A definitive statement regarding the effect of heater probe size would require the performance of a randomised trial in which patients with bleeding peptic ulcer were randomised to combination treatment with injection therapy and either the large or the small heater probe.

Chapter 8

Prediction of therapeutic failure

Introduction

Endoscopic therapy for bleeding peptic ulcer is successful in the majority of patients, but those patients in whom primary haemostasis is not achieved, or bleeding recurs are at an increased risk of death (Balanzo et al., 1988; Panes et al., 1987; Chung et al., 1998; Oxner et al., 1992; Moreto et al., 1992; Swain et al., 1986; Laine 1987)). Failure of primary haemostasis is readily apparent and in most cases the patient is referred for surgery. Secondary failure of endoscopic therapy (re-bleeding) is managed by repeat endoscopic therapy or surgery. There may be a significant time between the onset of further bleeding and the development of clinical signs of shock, haematemesis, melaena or a fall in haemoglobin. This plus the time involved in organising repeat endoscopy may result in delays in the diagnosis of re-bleeding and application of definitive therapy. Analysis of the data presented in this thesis, in common with those from multiple other randomised clinical trials, suggests that the haemostatic efficacy of endoscopic therapy is largely unrelated to the current methods employed, and that failure of endoscopic therapy occurs in 15-20% of patients. Accurate prediction of therapeutic failure in these high-risk patients could influence intensive monitoring and treatment strategies with the potential to improve overall outcome.

This chapter examines various clinical and endoscopic characteristics of the patients entered into the thrombin trial in order to define those associated with re-bleeding.

Method

All patients in whom primary haemostasis had been achieved were included. Re-bleeding was defined as described in Chapter 2.

Outcome following endoscopic therapy was analysed according to a number of clinical and endoscopic variables, with the trial patients divided into groups according to each of the following:

Age (≤ 60 vs > 60 years)

Presence of shock (yes vs no)

Presence of co-morbid disease (all category scores 0 or 1 vs ≥ score 2 or 3)

Haemoglobin (< 10g/dl vs ≥ 10g/dl)

Rockall score (< 6 vs ≥ 6)

Ulcer size (≤ 20mm vs > 20mm)

Bleed from a posterior duodenal ulcer (yes vs no)

Bleed from a high lesser curve gastric ulcer (yes vs no)

Presence of active bleeding (yes vs no)

For definitions of shock and classification of co-morbid disease see Chapter 2. Rockall score was calculated as in Table 1.1. The ulcer size was estimated by comparing the ulcer base to the length of the brass cylinder at the distal end of the heater probe tip (10mm). High lesser curve ulcers were those on the lesser curve of the stomach close to the cardia. Ulcers located in the duodenal bulb and positioned in the right side of the

endoscopic view between 12 o'clock and 6 o'clock relative to the gastric incisura were termed posterior duodenal ulcers.

Univariate analysis was used to assess the strength of association of each variable with the outcome of endoscopic therapy. This was undertaken by comparing the percentages of re-bleeds in the groups for each variable (e.g. haemoglobin <10g/dl and haemoglobin ≥10g/dl). Differences in percentages were analysed using the χ^2 test. Variables with p values less than 0.2 were then entered into a stepwise logistic regression model, and were considered to be significant independent predictors of outcome when $p < 0.05$. Data analysis was performed using the SPSS version 10 statistical package.

Results

Of the 247 patients entered into the trial, primary haemostasis was achieved in 239 (97%). Re-bleeding occurred in 36 patients. Three of these exsanguinated before definitive therapy could be carried out and one was unfit for further intervention. Twenty three patients underwent urgent surgery. Fifteen patients were managed by repeat endoscopic therapy and this was successful in six. In the remainder, re-bleeding was definitively controlled by surgical operation (Figure 9.1).

Univariate analysis of variables showed that re-bleeding was associated with moderate or severe co-morbid disease, Rockall score at least 6, ulcer size greater than 20mm and posterior duodenal ulcer (Table 9.1).

Figure 9.1 Outcome summary

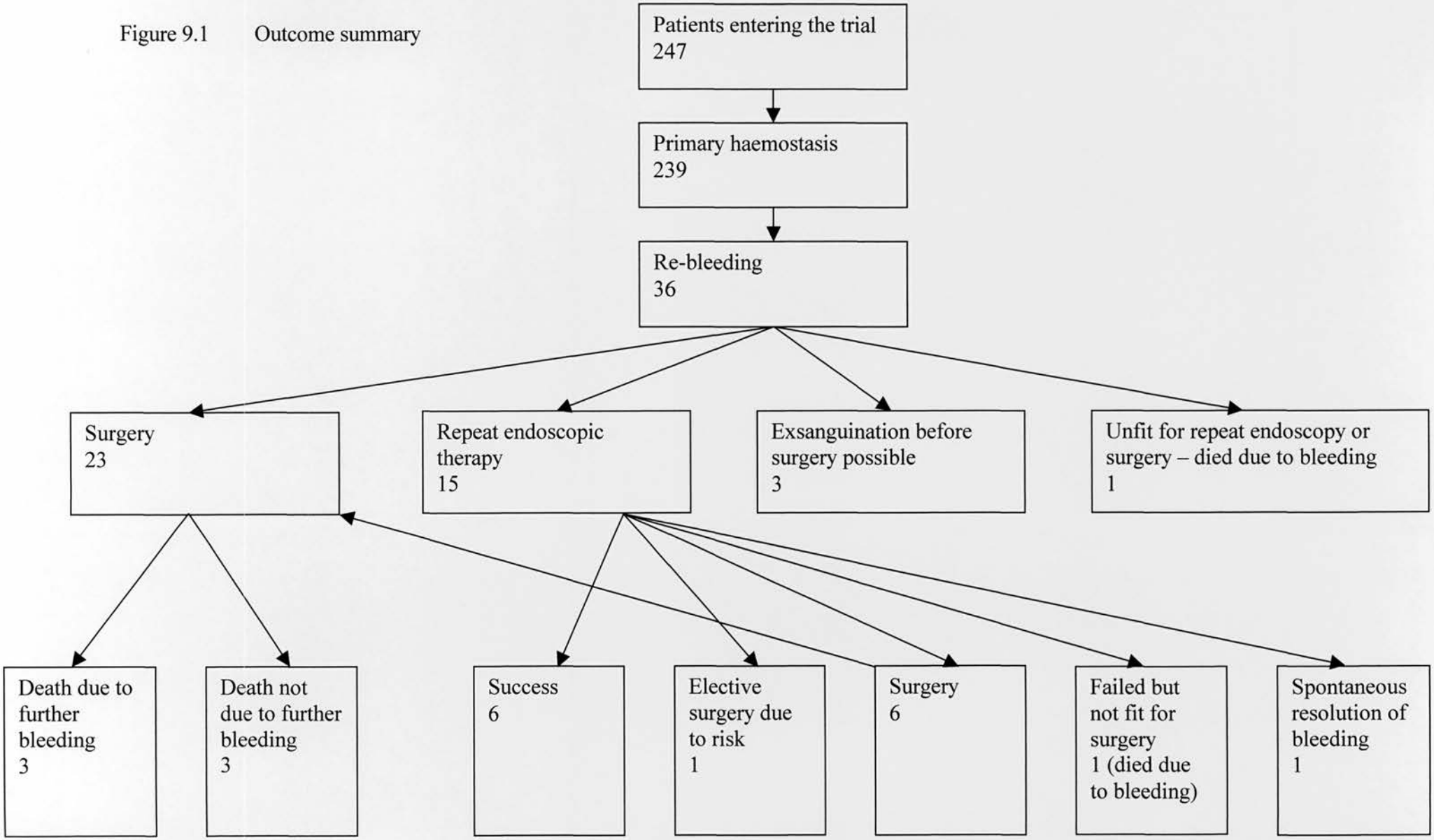


Table 9.1 Univariate analysis: factors related to re-bleeding

Predictor	Category	n	Re-bleed, n (%)	χ^2 test, p	OR (95% CI)
Age	≤ 60 years	67	9 (13)	0.36	1.00
	> 60 years	180	35 (19)		1.56 (0.70, 3.44)
Presence of shock	No	91	12 (13)	0.20	1.00
	Yes	156	32 (21)		1.70 (0.83, 3.49)
Presence of co-morbid disease	All no/mild	163	19 (12)	**0.001**	1.00
	≥1 mod/severe	84	25 (30)		3.21 (1.65, 6.27)
Rockall score	< 6	122	11 (9)	**0.02**	1.00
	≥ 6	125	25 (20)		2.52 (1.18, 5.39)
Haemoglobin	≥10g/dl	87	11 (12.6)	0.15	1.00
	<10g/dl	158	33 (20.9)		1.82 (0.87, 3.82)
Ulcer size	≤10mm	81	11 (13.6)	0.30	1.00
	>10mm	166	33 (19.9)		1.58 (0.75, 3.32)
Ulcer size	≤20mm	211	29 (13.7)	**<0.001**	1.00
	>20mm	36	15 (41.7)		4.48 (2.08, 9.68)
Posterior duodenal ulcer	No	184	24 (13.0)	**0.002**	1.00
	Yes	63	20 (31.7)		3.10 (1.57, 6.13)
High lesser curve gastric ulcer	No	216	40 (18.5)	0.61	1.00
	Yes	31	4 (12.9)		0.65 (0.22, 1.97)
Presence of active bleeding	No	154	26 (16.9)	0.75	1.00
	Yes	93	18 (19.4)		1.18 (0.61, 2.30)

Further analysis using multiple logistic regression revealed that the presence of moderate or severe co-morbid disease in any system, ulcer size greater than 20mm and the presence of a posterior duodenal ulcer were significant independent predictors of re-bleeding (Table 9.2).

Table 9.2 Multivariate analysis: factors related to re-bleeding

Significant independent predictors of re-bleed	Category	n*	Re-bleed, n (%)*	χ^2 test, p	OR (95% CI)
Ulcer size	≤20mm	211	29 (13.7)	0.002	1.00
	>20mm	36	15 (41.7)		3.57 (1.59, 8.03)
Presence of co-morbid disease	All no/mild	163	19 (11.7)	0.006	1.00
	≥1 mod/severe	84	25 (29.8)		2.68 (1.33, 5.41)
Posterior duodenal ulcer	No	184	24 (13.0)	0.012	1.00
	Yes	63	20 (31.7)		2.52 (1.22, 5.19)

* Percentages are based on those in the univariate analysis

Factors associated with failure of endoscopic therapy for bleeding peptic ulcer have been the subject of a number of published papers (Villanueva et al., 1993; Choudari et al., 1994; Hsu et al., 1994; Brullet et al., 1996 (Gut); Brullet et al., 1996 (Gastrointest Endosc); Chung IK et al., 2001; Wong et al., 2002). There are methodological differences between these studies and the current analysis, but the patient inclusion criteria are similar and my results are similar to those of others.

In Chapter 5 the presence of co-morbid disease was shown to be associated with re-bleeding, surgery and death. Neurological disease and malignancy were significant independent predictors of re-bleeding. Impaired wound healing and coagulation mechanisms may explain the association of co-morbid disease with re-bleeding. It is, therefore, not surprising that co-morbidity is a significant independent predictor of re-bleeding in this analysis. These results are similar to those of Villanueva et al (1993). This group noted that patients with co-morbid conditions were more likely to have larger ulcers, and ulcers in the posterior duodenum. This is also the case in my patients, but despite this, the effect of co-morbidity persisted after multivariate analysis. Other studies have not demonstrated co-morbid illness to be an independent predictor of re-bleeding, the effect on mortality being more significant (Brullet et al., 1996 (Gastrointest Endosc)).

Ulcer size is the most frequently reported predictor of re-bleeding. Ulcers greater than 20mm in diameter were significant independent predictors of failure of therapy in four

of the seven published papers. (Brullet et al., 1996; Brullet et al., 1996; Chung et al., 2001; Wong et al., 2002) A fifth paper found ulcer diameter greater than 10mm to predict failure. (Villanueva et al., 1993) Measurement of ulcer size may be subject to error, but in practice it is relatively straightforward to estimate the diameter of an ulcer base compared to the known length of the heater probe tip. This technique may not yield reproducible measurements correct to one or two millimetres, but will reliably differentiate large ulcers from small ones, and is the type of approach most readily applicable to routine clinical practice. Large ulcers are usually deeper and contain larger vessels than small ulcers. This may adversely affect outcome in three ways. Firstly, deep ulcers may be difficult to approach in order to adequately apply endoscopic therapy. Secondly, larger ulcers tend to be more chronic and fibrous, rendering endoscopic therapy more difficult to apply. Thirdly, endoscopic therapy has been shown to be less effective when applied to larger vessels (Hepworth et al., 1998).

Ulcer position has been shown to influence re-bleeding in three papers (Choudari et al., 1994; Villanueva et al., 1993; Chung et al., 2001). Choudari et al. found that the proportion of patients bleeding from a posterior duodenal ulcer was higher in those patients who re-bled after endoscopic therapy. This observation was not subjected to multivariate analysis. Chung et al. found that the presence of a gastric ulcer was predictive of re-bleeding, but again only in the univariate analysis. Only the paper by Villanueva et al. demonstrated the presence of a posterior duodenal ulcer to be predictive of re-bleeding after multivariate analysis. The association of posterior duodenal ulcer with poor outcome is logical because large ulcers in this area erode into branches of the posterior duodenal artery and produce severe bleeding. In addition, the

posterior part of the duodenal bulb is often difficult to approach, requiring tangential application of therapy and limiting the efficacy of certain therapeutic methods.

The accuracy of endoscopic localisation of a duodenal ulcer to a particular part of the bulb has been questioned by Straker et al. (1992). This study concluded that a single experienced endoscopist correctly identified the posterior duodenum in as few as 30% of cases. This observation was based on a series of only 20 patients in whom laparotomy was not performed to confirm the ulcer site, and the result has not been verified. I found the previously described system for localisation of the ulcer within the duodenal bulb straightforward, and in those patients undergoing surgery after failed endoscopic therapy the position of the ulcer documented by the endoscopist was correct in the majority, although the operation note did not state the exact position of the ulcer in all cases.

Whilst the positive findings of this analysis are not surprising, other factors which might have been expected to adversely affect the performance of endoscopic therapy were not independently associated with failure.

The presence of shock on admission has been reported as an independent predictor in three papers (Hsu et al., 1994; Brullet et al., 1996; Wong et al., 2002). In all these publications shock was deemed to be present only when hypotension was evident. In my patients the definition of shock was broader, including tachycardia as a marker of cardiovascular compromise. Thus the group with "shock" may have included patients

with less severe bleeding, resulting in a lack of effect for this variable in my patient group.

Active bleeding has also been shown to predict therapeutic failure in three previous reports (Brullet et al., 1996; Chung et al., 2001; Wong et al., 2002). Differences in the definition of active bleeding, interobserver variation in reporting of endoscopic stigmata and differences in the proportions of patients with spurting and oozing haemorrhage could all account for the differences between these analyses and my own.

Whilst older patients have a greater degree of co-morbid disease, age itself was not an independent factor predictive of therapeutic failure. Resection specimens of ulcers do not contain significant atheroma (Swain et al., 1986) and in the elderly the immediate response to haemostatic therapy is similar to that of younger patients. Increasing age was more closely linked to mortality.

This analysis demonstrated that endoscopic therapy is less effective in patients with co-morbid conditions, and in those who have bled from large posterior duodenal ulcers. In my patient group there were six patients with all these risk factors. Primary haemostasis was achieved in all patients but all re-bled. Five of these patients required surgery and two died. More intensive strategies such as elective repeat endoscopic therapy or even prophylactic surgical operation may be appropriate for these high-risk patients.

Chapter 9

Summary and Conclusions

A literature review (Chapter 1) reveals that several endoscopic therapies have been used to manage peptic ulcers. Injection agents are the most straightforward to use; they are portable and cheap. Thrombin injection is theoretically attractive and its use in combination with adrenaline is supported by a previous clinical trial. The trial reported in this thesis (Chapters 2-4), however, does not support the use of thrombin as an adjunct to the heater probe, as the results obtained are no better than those achieved with adjunctive placebo injection. Whilst it is unlikely that the placebo injection had significant haemostatic effects, a type 2 error could be present. No pharmacologically active compounds were present in the placebo solution, and the injected volumes were small. Although thrombin injection was not proven to be effective, neither did it have significant adverse effects. This includes a lack of demonstrable virus transmission, although the theoretical possibility exists of transmission of as yet unknown viruses or other infectious agents. The findings do not necessarily imply that thrombin injection is ineffective, but show that the combination of thrombin injection plus heater probe is not superior to heater probe plus placebo injection.

The heater probe is an effective and safe instrument. It can be particularly useful when therapy is applied tangentially. The high pressure washing jet and the ability to tamponade a bleeding vessel facilitate visualisation and initial control of the bleeding point. The analysis in this thesis (Chapter 7) suggests that the small diameter probe may be as effective as the larger probe when combined with endoscopic injection. Further studies are necessary to definitively address this question, since as stated in

Chapter 7 my study was a retrospective analysis with a low power and potential for a type 2 error.

My findings in relation to the Rockall scoring system (Chapter 5) were entirely expected. Endoscopic therapy improves outcome and, therefore the re-bleed and mortality rates predicted by the Rockall system are higher than those observed after thermal and injection therapy for bleeding ulcers. Despite this, the pattern of increasing re-bleed and mortality rates with increasing score persists. The system can be used to accurately predict mortality but not re-bleeding in patients who have received endoscopic therapy. ROC curve analysis suggests that patients scoring six or greater should be monitored closely in a high dependency area, whereas those with lower scores could be managed on a general ward. This has practical value and could be incorporated into local or national guidelines.

It is not surprising that co-morbid conditions have a major impact on both the success of endoscopic therapy and survival following an episode of major bleeding. Neurological conditions (predominantly acute stroke), respiratory disease, malignancy and renal failure were independently associated with poor outcome (Chapter 6). There may not have been sufficient numbers of patients in the study population with cardiovascular disease severe enough to affect outcome. The co-morbidity score discussed in this thesis requires refinement and validation. A detailed score categorising the severity of co-morbid disease would be a useful tool to enable investigators to properly compare study populations in different areas of the world.

Accurate prediction of failure of endoscopic therapy could allow those patients at highest risk to be offered semi-elective surgery after initial control of bleeding. Multiple studies have addressed the problem of prediction of failure of endoscopic therapy, but unfortunately consistent factors conferring a high-risk have not emerged. Re-bleeding is a relatively infrequent event even in high-risk patients, and the numbers of patients in the published trials is consequently small. My own analysis (Chapter 8) contains 36 patients, and the other seven published trials contain only a total of 324 patients. My findings - that re-bleeding occurs in patients with significant co-morbid disease and large ulcers located near large arteries - were consistent with those of most other studies. Since the majority of patients do not re-bleed after successful endoscopic therapy, and accurate predictive factors of poor outcome are not defined, the best policy remains one of close observation rather than semi-elective surgery in selected patients.

1. The most recent meta-analysis to study endoscopic therapy in general was published by Cook et al. in 1992. An up to date meta-analysis including the many recent trials is required.

2. None of the existing agents used for endoscopic injection have been shown to be better than dilute adrenaline. It is possible that a significant proportion of the effect of an endoscopic injection relates to tamponade of the bleeding vessel, but the current agents in use are rapidly cleared from the injection site. New agents which persist for a longer time may be more effective. One such agent is sodium hyaluronate. This has recently been used to facilitate en bloc resection of superficial gastric and colonic tumours (Yamamoto et al., 2003), and to endoscopically treat vesico-ureteric reflux in children (Kirsch et al., 2003). A pilot study using animal models of peptic ulcer bleeding is required in the first instance.

3. It is unlikely that the results of thermal methods of endoscopic therapy will improve sufficiently to make a major impact on outcome. I feel that future work on non-injection methods should be directed towards mechanical methods such as the haemoclip. Trial data are conflicting regarding the use of the haemoclip in its current form, but refinement of the mechanism of orientation, development of the newer three prong design and improvement in the force exerted by the closed clip may improve results.

4. A problem common to most trials of endoscopic therapy is that of small size. Multi-centre collaborative trials are required in order to include large numbers of patients and convincingly demonstrate effects on mortality. A national endoscopy research group could facilitate this aim.

5. A prospective evaluation of outcome following post-endoscopy placement and monitoring according to Rockall score is required.

6. A study to refine and validate the co-morbid disease score would be desirable.

7. New methods for prediction of failure of endoscopic therapy are required. Measurement of arterial blood flow in the base of an ulcer has been used to direct endoscopic therapy and to assess the results of therapy (Riemann and Rosenbaum, 2000). Development of this technique may identify patients in whom blood flow persists after apparently successful endoscopic treatment.

References

Antonioli A, Gandolfo M, Rigo GP et al. Somatostatin and cimetidine in the control of acute upper gastrointestinal bleeding. A controlled multicentre study. Hepato-gastroenterol 1986; 33: 71–74.

Avery Jones F. Haematemesis and melaena with special reference to bleeding peptic ulcer. Br Med J 1947; ii: 441–446.

Balanzo J, Sainz S, Such J, et al. Endoscopic hemostasis by local injection of epinephrine and polidocanol in bleeding ulcer; a prospective, randomized trial. Endoscopy 1988; 20: 289-291.

Barer D, Ogilvie A, Henry D et al. Cimetidine and tranexamic acid in the treatment of acute upper-gastrointestinal-tract bleeding. N Engl J Med 1983; 308 (26): 1571–1575.

Basso N, Bagarani M, Bracci F et al. Ranitidine and somatostatin. Their effects on bleeding from the upper gastrointestinal tract. Arch Surg 1986; 121: 833–835.

Beneditti G, Sablich R, Lacchin T. Endoscopic injection sclerotherapy in non-variceal upper gastrointestinal bleeding. A comparative study of epinephrine and thrombin. Endoscopy 1990; 22: 157–159.

Bennet B, Dawson AA, Gibson BS et al. Study of viral safety of Scottish National Blood Transfusion Service factor VIII/IX concentrate. Transfusion Medicine 1993; 3: 295-298.

Binmoeller KF, Thonke F, Soehendra N. Endoscopic hemoclip treatment for gastrointestinal bleeding. Endoscopy 1993; 25(2): 167-170.

Blatchford O, Murray WR, Blatchford M. A risk score to predict need for treatment for upper gastro-intestinal haemorrhage. Lancet 2000; 356: 1318-21.

Bleau BL, Gostout CJ, Sherman KE et al. Recurrent bleeding from peptic ulcer associated with adherent clot: a randomized study comparing endoscopic treatment with medical therapy. Gastrointest Endosc 2002; 56(1): 1-6.

Bornman PC, Theodorou N, Shuttleworth RD et al. Importance of hypovolaemic shock and endoscopic signs in predicting recurrent haemorrhage from peptic ulceration: a prospective evaluation. Br Med J 1985; 291: 245–247.

Brearley S, Hawker PC, Dykes PW et al. Peri-endoscopic bipolar diathermy coagulation of visible vessels using a 3.2 mm probe – a randomised clinical trial. Endoscopy 1987; 19: 160–163.

Brullet E, Calvet X, Campo R et al. Factors predicting failure of endoscopic injection therapy in bleeding duodenal ulcer. Gastrointest Endosc 1996; 43: 111-116.

Brullet E, Campo R, Calvet X et al. Factors related to the failure of endoscopic injection therapy for bleeding gastric ulcer. Gut 1996; 39: 155-158.

Buset M, Des Marez B, Vandermeeran A. Laser therapy for non bleeding visible vessel in peptic ulcer haemorrhage: a prospective randomised study. Gastrointest Endosc 1988; 34: 173.

Carter R, Anderson JR. Randomised trial of adrenaline injection and laser photocoagulation in the control of haemorrhage from peptic ulcer. Br J Surg 1994; 81: 869–871.

Chiozzini G, Bortoluzzi F, Pallini P et al. Controlled trial of absolute ethanol vs epinephrine as injection agent in gastroduodenal bleeding. Gastroenterology 1989; 96: A86.

Chiu PWY, Lam CYW, Lee SW et al. Effect of scheduled second therapeutic endoscopy on peptic ulcer re-bleeding: a prospective randomized trial. Gut 2003; 52: 1403-1407.

Chiu PWY, Lau TS, Kwong KH et al. Impact of programmed second endoscopy with appropriate re-treatment on peptic ulcer re-bleeding: A systematic review. Ann Coll Surg 2003; 7: 106-115.

Choudari CP, Palmer KR. Endoscopic injection therapy for bleeding peptic ulcer: a comparison of adrenaline alone with adrenaline plus ethanolamine oleate. Gut 1994; 35: 608–610.

Choudari CP, Rajgopal C, Elton RA et al. Failures of endoscopic therapy for bleeding peptic ulcers; an analysis of risk factors. Am J Gastroenterol 1994; 89: 1968–1972.

Choudari CP, Rajgopal C, Palmer KR. Comparison of endoscopic injection therapy versus the heater probe in major peptic ulcer haemorrhage. Gut 1992; 33 (9): 1159–1161.

Christiansen J, Ottenjann R, Von Arx F. Placebo-controlled trial with the somatostatin analogue sms 201-995 in peptic ulcer bleeding. Gastroenterology 1989; 97: 568–574.

Chung IK, Ham JS, Kim HS et al. Comparison of the hemostatic efficacy of the endoscopic hemoclip method with hypertonic saline-epinephrine injection and a combination of the two for the management of bleeding peptic ulcers. Gastrointest Endosc 1999; 49(1): 13-18.

Chung IK, Kim EJ, Lee MS et al. Endoscopic factors predisposing to rebleeding following endoscopic hemostasis in bleeding peptic ulcers. Endoscopy 2001; 33(11): 969-975.

Chung SC, Leong HT, Chan AC et al. Epinephrine or epinephrine plus alcohol for injection of bleeding ulcers; a prospective randomized trial. Gastrointest Endosc 1996; 43(6): 591-595.

Chung SCS, Lau JY, Sung JJ et al. Randomised comparison between adrenaline injection alone and adrenaline injection plus heat probe treatment for actively bleeding peptic ulcers. Br Med J 1997; 314: 1307–1311.

Chung SCS, Leung JWC, Steele RJC et al. Endoscopic injection of adrenaline for actively bleeding ulcers: a randomized trial. Br Med J 1988; 296: 1631-1633.

Chung SCS, Leung JWC, Sung JY et al. Injection or heat probe for bleeding ulcer? Gastroenterology 1991; 100: 33–37.

Church NI and Palmer KR. Relevance of the Rockall Score in patients undergoing endoscopic therapy for peptic ulcer haemorrhage. Eur J Gastroenterol Hepatol 2001; 13(10): 1149-1152.

Cipoletta L, Bianco MA, Marmo R et al. Endoclips versus heater probe in preventing early recurrent bleeding from peptic ulcer: a prospective and randomized trial. Gastrointest Endosc 2001; 53: 147-1451.

Cipolletta L, Bianco MA, Rotondano G et al. Prospective comparison of argon plasma coagulator and heater probe in the endoscopic treatment of major peptic ulcer bleeding. Gastrointest Endosc 1998; 48 (2): 191–195.

Collins R, Langman M. Treatment with histamine H_2 antagonists in acute upper gastrointestinal haemorrhage: implications of randomised trials. N Engl J Med 1985; 313: 660–666.

Cook DJ, Guyatt GH, Salena BJ et al. Endoscopic therapy for acute non-variceal haemorrhage: a meta-analysis. Gastroenterology 1992; 102: 139–148.

Coraggio F, Bertini G, Catalona A et al. Clinical controlled trial of somatostatin with ranitidine and placebo in the control of peptic haemorrhage of the upper gastrointestinal tract. Digestion 1989; 43: 190–195.

Coraggio F, Scarpato P, Spina M, Lombardi S. Somatostatin and ranitidine in the control of iatrogenic haemorrhage of the upper gastrointestinal tract. Br Med J Clinical research Ed 1984; 289 (6439): 224.

Daneshmend TK, Hawkey CJ, Langman MJS et al. Omeprazole versus placebo for acute upper gastrointestinal bleeding: randomised double blind controlled trial. Br Med J 1992; 304: 143–147.

Fleig WE. Solute or solvent: does water do the haemostatic job? Endoscopy 1994; 26: 362-363.

Fleischer D. Etiology and prevalence of severe persistent upper gastrointestinal bleeding. Gastroenterology 1983; 84: 538–543.

Fullarton GM, Birnie GG, MacDonald A et al. Controlled trial of heater probe treatment in bleeding peptic ulcers. Br J Surg 1989; 76: 541–544.

Galmiche JP, Cassigneul J, Faivre J et al. Somatostatin in peptic ulcer bleeding. Results of a double blind controlled trial. Int J Clin Pharmacol Res 1983; III: 379–387.

Garripoli A, Mondardini A, Turco D et al. Hospitalization for peptic ulcer bleeding: evaluation of a risk scoring system in clinical practice. Digestive & Liver Disease 2000; 32(7): 577-582.

Gevers AM, De Goede E, Simoens M et al. A randomized trial comparing injection therapy with hemoclip and with injection combined with hemoclip for bleeding ulcers. Gastrointest Endosc 2002; 55(4): 466-469.

Gisbert JP, Gonzalez L, Calvet X et al. Proton pump inhibitors versus H2-antagonists: a meta-analysis of their efficacy in treating bleeding peptic ulcer. Alimentary Pharmacology and Therapeutics 2001; 15(7): 917-926.

Goldstein DS. The electrocardiogram in stroke: relationship to pathophysiological type and comparison with prior tracings. Stroke 1979; 10: 253-259.

Goletti O, Sidoti F, Lippolis PV et al. Omeprazole versus ranitidine and somatostatin in the treatment of acute severe gastroduodenal haemorrhage. Br J Surg 1992; 79 (Suppl): S123.

Graor RA, Hetzer NR. Management of coexistent carotid artery and coronary artery disease. Stroke 1988; 19: 1441-1444.

Griffiths WJ, Neumann DA, Welsh DA. The visible vessels as an indicator of uncontrolled or recurrent gastrointestinal haemorrhage. N Engl J Med 1979; 300: 1411–1413.

Guglielmi A, Ruzzenente A, Sandri M et al. Risk assessment and prediction of rebleeding in bleeding gastroduodenal ulcer. Endoscopy 2002; 34(10): 778-786.

Hasselgren G, Keelan M, Kirdeikis P et al. Optimization of acid suppression for patients with peptic ulcer bleeding: an intragastric pH-metry study with omeprazole. Eur J Gastroenterol Hepatol 1998; 10: 601-606.

Hasselgren G, Lind T, Lundell L et al. Continuous intravenous infusion of omeprazole in elderly patients with peptic ulcer bleeding: results of a placebo controlled multicentre study. Scand J Gastroenterol 1997; 32 (4): 328-333.

Hayashi T, Yonezawa M, Kawabara T. The study on staunch clip for the treatment by endoscopy. Gastroenterol Endosc 1975; 17; 92-101.

Heldwein W, Avenhaus W, Schonekas H, et al. Injection of fibrin tissue adhesive versus laser photocoagulation in the treatment of high risk bleeding peptic ulcers: a controlled randomised study. Endoscopy 1996; 28(9): 756-760.

Henry DA, O'Connell DL. Effect of fibrinolytic inhibitors on mortality from upper gastrointestinal haemorrhage. Br Med J 1989; 298: 1142–1146.

Henry DA, White I. Endoscopic coagulation for gastrointestinal bleeding. N Engl J Med 1988; 318: 186–187.

Hepworth CC, Kadirkamanathan SS, Gong F, Swain CP. A randomised controlled comparison of injection, thermal, and mechanical endoscopic methods of haemostasis on mesenteric vessels. Gut 1998; 42: 462-469.

Holman RAE, Davis M, Gough KR et al. Value of centralised approach in the management of haematemesis and melaena: Experience in a district general hospital. Gut 1990; 31: 504–508.

Homer AC, Powell S, Vacary FR. Is Nd-YAG laser treatment for upper gastrointestinal bleeds of benefit in a district general hospital? Postgrad Med J 1985; 61: 19–22.

Horowitz B, Prince AM, Horowitz MS, Watklevicz C. Viral safety of solvent-detergent treated blood products. Virological Safety Aspects of Plasma Derivatives. In: Brown F, ed. Developments in Biological Standardization. Vol 81. Basel: Karger, 1993: 147-161.

Hsu PI, Lin XZ, Chan SH et al. Bleeding peptic ulcer – risk factors for rebleeding and sequential changes in endoscopic findings. Gut 1994; 35: 746-749.

Imperiale TF, Birgisson S. Somatostatin or octreotide compares with H_2 antagonists and placebo in the management of acute non-variceal upper gastrointestinal haemorrhage: a meta-analysis. Ann Intern Med 1997; 127: 1062–1071.

Jaramillo JL, Carmona C, Galvez C et al. Efficacy of the heater probe in peptic ulcer with a non-bleeding visible vessel. A controlled randomised study. Gut 1993; 34: 1502-1506.

Javid G, Masoodi I, Zargar SA et al. Omeprazole as adjuvant therapy to endoscopic combination injection sclerotherapy for treating bleeding peptic ulcer. American Journal of Medicine 2001; 111(4): 280-284.

Jenkins SA, Poulianos G, Coraggio F et al. Somatostatin in the treatment of non-variceal upper gastrointestinal bleeding. Dig Dis Sci 1998; 16: 214–224.

Jensen DM, Kovacs TOG, Jutabha R et al. Randomized trial of medical or endoscopic therapy to prevent recurrent ulcer hemorrhage in patients with adherent clots. Gastroenterology 2002; 123(2): 407-413.

Jensen DM, Machicado GA, Kovacs TOG. Controlled randomised study of heater probe and BICAP for haemostasis of severe ulcer bleeding. Gastroenterology 1988; 94: A208.

Jensen DM, Machicado GA, Tapia JI et al. Controlled trial of endoscopic argon laser for severe ulcer haemorrhage. Gastroenterology 1984; 86: 1125.

Jensen DM, Tapia JI, Machicado GA et al. Endoscopic heater and multipolar probes for treatment of bleeding canine gastric ulcers. Gastrointest Endosc 1982; 29: 151.

Johnston J, Jensen D, Auth D et al. Comparison of endoscopic lasers, electrosurgery and the heater probe in coagulation of canine arteries. Gastrointest Endosc 1984; 30: 154.

Johnston J, Rawson S, Namihara Y. Experimental comparison of heater probe and BICAP for endoscopic treatment of gastrointestinal bleeding. Gastrointest Endosc 1985; 31: 155-156.

Johnston JH, Jensen DM, Auth D. Experimental comparison of endoscopic yttrium-aluminium-garnet laser, electrosurgery and heater probe for canine gut arterial coagulation. Gastroenterology 1987; 92: 1101-1108.

Johnston JH, Sones JQ, Long BW, Posey EL. Comparison of heater probe and YAG laser in treatment of major bleeding from peptic ulcers. Gastrointest Endosc 1985; 31: 175-180.

Kayasseh L, Gyr K, Keller U et al. Somatostatin and cimetidine in peptic ulcer haemorrhage. A randomised controlled trial. Lancet 1980; i: 844–846.

Khuroo MS, Yattoo GN, Javid G et al. A comparison of omeprazole and placebo for bleeding peptic ulcer. N Engl J Med 1997; 336: 1054–1058.

Kirsch AJ. Perez-Brayfield MR. Scherz HC. Minimally invasive treatment of vesicoureteral reflux with endoscopic injection of dextranomer/hyaluronic acid copolymer: the Children's Hospitals of Atlanta experience. Journal of Urology 2003; 170(1): 211-215.

Knobl P, Lechner K. Acquired factor V inhibitors. Ballieres Clin Haematol 1998; 11: 305-318.

Krejs GJ, Little KH, Westergaard H. Laser photocoagulation for the treatment of acute peptic ulcer bleeding. N Engl J Med 1987; 316: 1618–1621.

Kubba AK, Lessells A, Palmer KR. Experimental studies of injection therapy for ulcer haemorrhage in rabbits. Br J Surg 1997; 84: 551-554.

Kubba AK, Murphy W, Palmer KR. Endoscopic injection for bleeding peptic ulcer: a comparison of adrenaline with adrenaline plus human thrombin. Gastroenterology 1996; 111: 623–628.

Lai KC, Swain CP. The size of vessel in patients dying from bleeding gastric ulcer. Gastroenterology 1993; 104: A202.

Lai KH, Peng SN, and Guo WS et al. Endoscopic injection for the treatment of bleeding ulcers: local tamponade or drug effect? Endoscopy 1994; 26: 338-341.

Laine L, Estrada R. Randomized trial of normal saline solution injection versus bipolar electrocoagulation for treatment of patients with high-risk bleeding ulcers: is local tamponade enough? Gastrointest Endosc 2002; 55(1): 6-10.

Laine L. Multipolar electrocoagulation for the treatment of ulcers with non-bleeding visible vessels: a prospective, controlled trial. Gastroenterology 1988; 94: A246.

Laine L. Multipolar electrocoagulation in the treatment of active upper gastrointestinal hemorrhage: a prospective controlled trial. N Engl J Med 1987; 316: 1613-1617.

Laine L. Multipolar electrocoagulation versus injection therapy in the treatment of bleeding peptic ulcers. Gastroenterology 1990; 99: 1303–1306.

Lau JYW, Sung JJY, Lam Y et al. Endoscopic retreatment compared with surgery in patients with recurrent bleeding after initial endoscopic control of bleeding ulcers. N Engl J Med 1999; 340: 751–756.

Lau JYW, Sung JY, Lee KKC et al. Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. N Engl J Med 2000; 343: 310-316.

Lazo MD, Andrade R, Medina MC et al. Effect of injection sclerosis with alcohol on the rebleeding rate of gastroduodenal peptic ulcers with nonbleeding visible vessels: a prospective, controlled trial. Am J Gastroenterol 1992; 87 (7): 843–846.

Lemeshow S, Le Gall J. Modeling the severity of illness of ICU patients. JAMA 1994; 272: 1049-1055.

Levy J, Khakoo S, Barton R et al. Fatal injection sclerotherapy of a bleeding peptic ulcer. Lancet 1991; 337: 504 (letter).

Lin HJ, Hsieh YH, Tseng GY et al. A prospective, randomized trial of large- versus small-volume endoscopic injection of epinephrine for peptic ulcer bleeding. Gastrointest Endosc 2002; 55(6): 615-619.

Lin HJ, Hsieh YH, Tseng GY et al. A prospective, randomized trial of endoscopic hemoclip versus heater probe thermocoagulation for peptic ulcer bleeding. Am J Gastroenterol 2002; 97: 2250-2254.

Lin HJ, Lee FY, Kang WM et al. Heat probe thermocoagulation and pure alcohol injection in massive peptic ulcer haemorrhage: a prospective, randomised controlled trial. Gut 1990; 31: 753–757.

Lin HJ, Lo WC, Lee FY et al. A prospective randomised comparative trial showing that omeprazole prevents rebleeding in patients with bleeding peptic ulcer after successful endoscopic therapy. Arch Intern Med 1998; 158: 54-58.

Lin HJ, Perng CL, Lee FY et al. Endoscopic injection for the arrest of peptic ulcer hemorrhage: final results of a prospective, randomized comparative trial. Gastrointest Endosc 1993; 39(1): 15-19.

Lin HJ, Perng CL, Sun IC, Tseng GY. Endoscopic hemoclip versus heater probe thermocoagulation plus hypertonic saline-epinephrine injection for peptic ulcer bleeding. Dig Liver Dis 2003; 35(12): 898-902.

Lin HJ, Tsai YT, Lee SD et al. A prospectively randomised trial of heat probe thermocoagulation versus pure alcohol injection in nonvariceal peptic ulcer haemorrhage. Am J Gastroenterol 1988; 83 (3): 283–286.

Lin HJ, Tseng GY, Perng CL et al. Comparison of adrenaline injection and bipolar electrocoagulation for the arrest of peptic ulcer bleeding. Gut 1999; 44: 715-719.

Lin HJ, Wang K, Perng CL et al. Natural history of bleeding peptic ulcers with a tightly adherent blood clot: a prospective observation. Gastrointest Endosc 1996; 43: 470-473.

Llach J, Bordas JM, Salmeron JM et al. A prospective randomised trial of heater probe thermocoagulation versus injection therapy in peptic ulcer haemorrhage. Gastrointest Endosc 1996; 43 (2 Pt 1): 117–120.

Loperfido S, Patelli G, La Torre L. Extensive necrosis of gastric mucosa following injection therapy of a bleeding peptic ulcer. Endoscopy 1990; 22: 785–786 (letter).

Macleod I, Mills PR, Mackenzie JF. Neodymium yttrium aluminium garnet laser photocoagulation for major haemorrhage from peptic ulcers and single vessels. Br Med J 1983; 286: 345–358.

Magnusson I, Ihre T, Johansson C et al. Randomised double blind trial of somatostatin in the treatment of massive upper gastrointestinal haemorrhage. Gut 1985; 26: 221–226.

Marmo R, Rotondano G, Bianco MA et al. Outcome of endoscopic treatment for peptic ulcer bleeding: Is a second look necessary? A meta-analysis. Gastrointest Endosc 2003; 57: 62-67.

Matthewson K, Swain CP, Bland M et al. Randomised comparison of Nd-YAG laser, heater probe and no endoscopic therapy for bleeding peptic ulcers. Gastroenterology 1990; 98: 1234–1244.

Messmann H, Schaller P, Andus T et al. Effect of programmed endoscopic follow-up examinations on the rebleeding rate of gastric or duodenal peptic ulcers treated by injection therapy: a prospective, randomised controlled trial. Endoscopy 1998; 30(7): 583-589.

Michaeletz PA, Judge D. Microwave energy compared with heater probe and BICAP in canine models of peptic ulcer hemorrhage. Gastroenterology 1989; 97: 676-684.

Moreto M, Zaballa M, Suarez MJ, et al. Endoscopic local injection of ethanolamine oleate and thrombin as an effective treatment for bleeding duodenal ulcer: a controlled trial. Gut 1992; 33: 456-459.

Morris DL, Brearly S, Thompson H et al. A comparison of the efficacy and depth of gastric wall injury with the 3.2- and 2.3-mm bipolar probes in canine arterial hemorrhage. Gastrointest Endosc 1985; 31: 361-363.

Nagayama K, Tazawa J, Sakai Y et al. Efficacy of Endoscopic Clipping for Bleeding Gastroduodenal Ulcer: Comparison with Topical Ethanol Injection. Am J Gastroenterol 1999; 94: 2897-2901.

Nakagawa K, Asaki S, Sato T. Endoscopic treatment of bleeding peptic ulcers. World Journal of Surgery 1989; 13(2): 154-157.

O'Brien JR. Some effects of adrenaline and anti-adrenaline compounds on platelets in vitro and in vivo. Nature 1963; 200: 763-764

O'Brien JD, Day SJ, Burnham WR. Controlled trial of small bipolar probes in bleeding peptic ulcers. Lancet 1986; 1: 464–468.

Oppenheimer S, Norris JW. Cardiac manifestations of acute neurological lesions. In Aminoff MJ (Ed), Neurology and General Medicine, Churchill-Livingston 1995, p 183.

Oxner RBG, Simmonds NJ, Gertner DJ et al. Controlled trial of endoscopic injection treatment for bleeding peptic ulcers with visible vessels. Lancet 1992; 339: 966–968.

Panes J, Viver J, Forme M, et al. Controlled trial of endoscopic sclerosis in bleeding peptic ulcers. Lancet 1987; 2(8571): 1292-1294.

Papp JP. Heat probe versus BICAP in the treatment of upper gastrointestinal bleeding. Am J Gastroenterol 1987; 82: 619–621.

Pascu O, Draghici A, Acalovschi I. The effect of endoscopic haemostasis with alcohol on the mortality rate of non-variceal upper gastrointestinal haemorrhage: a randomised prospective study. Endoscopy 1989; 21: 53–55.

Patchett SE, Enright l, Afdhal N et al. Clot lysis by gastric juice; an in vitro study. Gut 1989; 30: 1704–1707.

Pescatore P, Jornod P, Borovicka J et al. Epinephrine versus epinephrine plus fibrin glue injection in peptic ulcer bleeding: a prospective randomized trial. Gastrointest Endosc 2002; 55: 348-353.

Pescatore P, Verbeke C, Harle M, Manegold BC. Fibrin sealing in peptic ulcer bleeding: the fate of the clot. Endoscopy 1998; 30(6): 519-523.

Pimpl W, Boeckl O, Waclawiczek HW, Heinerman M. Estimation of the mortality rate of patients with severe gastrointestinal haemorrhage with the aid of a new scoring system. Endoscopy 1987; 19: 101-106.

Prescott RJ, Counsell CE, Gillespie WJ et al. Factors that limit the quality, number and progress of randomised controlled trials. Health Technol Assess 1999; 3 (20): 1-153.

Protell RL, Rubin CE, Auth DC et al. The heater probe: a new endoscopic method for stopping massive gastrointestinal bleeding. Gastroenterology 1978; 74: 257-262.

Pulanic R, Vucelic B, Rosandic M et al. Comparison of injection sclerotherapy and laser photocoagulation for bleeding peptic ulcers. Endoscopy 1995; 27 (4): 291–297.

Rajgopal C, Lessells A, Palmer KR. Mechanism of action of injection therapy for bleeding peptic ulcer. Br J Surg 1992; 79: 782-784.

Rajgopal C, Palmer KR. Endoscopic injection sclerosis: effective treatment for bleeding peptic ulcer. Gut 1991; 32: 727–729.

Randall GM, Jensen DM, Hirabayashi K et al. Controlled study of different sclerosing agents for coagulation of canine gut arteries. Gastroenterology 1989; 96: 1274-1281.

Rem JA, Hachinski VC, Boughner MD, Barnett HJM. Value of cardiac monitoring and echocardiography in TIA and stroke patients. Stroke 1985; 16: 950-956.

Rhode H, Thon K, Fischer M. Results of a defined concept of endoscopic Nd-YAG laser therapy in patients with upper gastrointestinal bleeding. Br J Surg 1980; 67: 360.

Riemann JF. Rosenbaum A. The role of Doppler ultrasound in gastrointestinal bleeding. Best Practice & Research in Clinical Gastroenterology 2000; 14(3): 495-504.

Rizza CR, Fletcher ML, Kernoff PB. Confirmation of viral safety of dry heat treated factor VIII concentrate (8Y) prepared by Bio Products Laboratory (BPL): a report on behalf of UK Haemophilia Centre Directors. Brit J Haematology 1993; 84: 269-272.

Rockall TA, Logan RFA, Devlin HB, Northfield TC. Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. Br Med J 1995; 311: 222–226.

Rockall TA, Logan RFA, Devlin HB, Northfield TC. Risk assessment after acute upper gastrointestinal haemorrhage. Gut 1996; 38: 316–321.

Rockall TA, Logan RFA, Devlin HB, Northfield TC. Selection of patients for early discharge or outpatient care after acute upper gastrointestinal haemorrhage. Lancet 1996; 347: 1138-1140.

Rockall TA, Logan RFA, Devlin HB, Northfield TC. Variation in outcome after acute upper gastrointestinal haemorrhage. Lancet 1995; 346: 346-350.

Rutgeerts P, Geboes K, Vantrappen G. Experimental studies of injection therapy for severe nonvariceal bleeding in dogs. Gastroenterology 1989; 97: 601–621.

Rutgeerts P, Rauws E, Wara P et al. Randomised trial of single and repeated fibrin glue compared with injection of polidocanol in treatment of bleeding peptic ulcer. Lancet 1997; 350: 692–696.

Rutgeerts P, Vantrappen G, Brockaert L et al. Comparison of endoscopic polidocanol injection and YAG laser for bleeding peptic ulcers. Lancet 1989; i: 1164–1167.

Rutgeerts P, Vantrappen G, Broeckhaert L et al. Controlled trial of YAG laser treatment of upper digestive haemorrhage. Gastroenterology 1982; 83: 410–416.

Saeed ZA, Cole RA, Ramirez FC et al. Endoscopic retreatment after successful initial hemostasis prevents ulcer rebleeding: a prospective randomized trial. Endoscopy 1996; 28(3): 288-294.

Saeed ZA, Ramirez FC, Hepps KS et al. Prospective validation of the Baylor bleeding score for predicting the likelihood of rebleeding after endoscopic haemostasis of peptic ulcers. Gastrointest Endosc 1995; 41: 561-565.

Saeed ZA, Winchester CB, Michaletz PA et al. A scoring system to predict rebleeding after endoscopic therapy of nonvariceal upper gastrointestinal haemorrhage, with a comparison of heat probe and ethanol injection. Am J Gastroenterol 1993; 88 (11): 1842–1849.

Sallah S, Wan JY. Inhibitors against factor VIII in patients with cancer. Analysis of 41 patients. Cancer 2001; 91: 1067-1074.

Sanderson JD, Taylor RFH, Pugh S et al. Specialised gastrointestinal units for the management of upper gastrointestinal bleeding. Postgrad Med J 1990; 66: 654–656.

Saperas E, Pique JM, Perez-Ayuso R et al. Somatostatin compared with cimetidine in the treatment of bleeding peptic ulcer without visible vessel. Aliment Pharmacol Ther 1988; 2(2): 153–159.

Schaffalitzky de Muckadell OB, Havelund T, Harling H et al. Effect of omeprazole on the outcome of endoscopically treated bleeding peptic ulcers: randomized double blind placebo controlled multicenter study. Scand J Gastroenterol 1997; 32 (4): 320–327.

Skok P, Ceranic D, Sinkovic A, Pocajt M. Peptic ulcer hemorrhage: argon plasma coagulation versus injection sclerotherapy: a prospective, randomized, controlled study. Verdauungskrankheiten 2001; 19(3): 107-113.

Sommerville KW, Henry DA, Davies JG et al. Somatostatin in treatment of haematemesis and melaena. Lancet 1985; i: 130–132.

Spiegel BM, Ofman JJ, Woods K, Vakil MB. Minimizing recurrent peptic ulcer hemorrhage after endoscopic hemostasis: the cost effectiveness of competing strategies. Am J gastroenterol 2002; 98(1): 86-97.

Straker RJ, Bienvenu JC, Nord HJ. Endoscopic orientation within the duodenal bulb. Endoscopy 1992; 24: 266-267.

Strohm WD, Rommele UE, Barton E et al. Injection therapy of bleeding ulcers with fibrin or polidocanol. Dtsch Med Wochenschr 1994; 119: 249–256.

Swain CP, Bown SG, Storey DW et al. Controlled trial of argon laser photocoagulation in bleeding peptic ulcer. Lancet 1981; 2(8259): 1313–1316.

Swain CP, Kirkham JS, Salmon PR, et al. Controlled trial of Nd-YAG laser photocoagulation in bleeding peptic ulcers. Lancet 1986; 1(8490): 1113-1117.

Swain CP, Mills TN, Shemesh E et al. Which electrode? A comparison of four endoscopic methods of electrocoagulation in experimental bleeding ulcers. Gut 1984; 25: 1424-1431.

Swain CP, Storey DW, Bown SG et al. Nature of the bleeding vessel in recurrently bleeding gastric ulcers. Gastroenterology 1986; 90: 595-608.

Torres AJ, Landa I, Hernandez F et al. Somatostatin in the treatment of severe upper gastrointestinal bleeding: a multicentre controlled trial. Br J Surg 1986; 73: 786–789.

Trudeau W, Siepler JK, Ross K et al. Endoscopic Nd-YAG laser photocoagulation of bleeding ulcers with visible vessels. Gastrointest Endosc 1985; 31: 138.

Tulassay Z, Gupta R, Papp J et al. Somatostatin versus cimetidine in the treatment of actively bleeding duodenal ulcer: a prospective, randomised, controlled trial. Am J Gastroenterol 1989; 84: 6–9.

Udd M, Mietinnen P, Palmu A et al. Regular-dose versus high-dose omeprazole in peptic ulcer bleeding: a prospective randomized double-blind study. Scand J Gastroenterol 2001; 36(12): 1332-1338.

Vallon AG, Cotton PB, Laurence BH et al. Randomised trial of endoscopic argon laser photocoagulation in bleeding peptic ulcers. Gut 1981; 22: 228–233.

Villanueva C, Balanzo C, Espinos JC. Endoscopic injection therapy of bleeding ulcer: a prospective and randomised comparison of adrenaline alone or with polidocanol. J Clin Gastroenterol 1993; 17: 195–200.

Villanueva C, Balanzo J, Espinos JC et al. Prediction of therapeutic failure in patients with bleeding peptic ulcer treated with endoscopic injection. Dig Dis Sci 1993; 38(11): 2062-2070.

Villanueva C, Balanzo J, Torras X et al. Omeprazole versus ranitidine as adjunct therapy to endoscopic injection in actively bleeding ulcers: a prospective randomized study. Endoscopy 1995; 27: 308-312.

Villanueva C, Balanzo J, Torras X et al. Value of second-look endoscopy after injection therapy for bleeding peptic ulcer: a prospective and randomized trial. Gastrointest Endosc 1994; 40(1): 34-39.

Vreeburg EM, Terwee CB, Snel P et al. Validation of the Rockall risk scoring system in upper gastrointestinal bleeding. Gut 1999; 44: 331–335.

Wagner PK, Rothmund M, Gronniger J. Secretin and somatostatin in treatment of acute upper gastrointestinal haemorrhage: a randomised trial. Klin Wochenschr 1983; 61: 285–289.

Walt RP, Cottrell J, Mann SG et al. Continuous intravenous famotidine for haemorrhage from peptic ulcer. Lancet 1992; 340: 1058–1062.

Wong SKH, Yu L-M, Lau JYW et al. Prediction of therapeutic failure after adrenaline injection plus heater probe treatment in patients with bleeding peptic ulcer. Gut 2002; 50: 322-325.

Yamamoto H. Kawata H. Sunada K et al. Successful en-bloc resection of large superficial tumors in the stomach and colon using sodium hyaluronate and small-caliber-tip transparent hood. Endoscopy 2003; 35(8): 690-694.

Yokohata T, Takeshima H, Fukushima R et al. Limitations of Endoscopic Injection Therapy and efficacy of Endoscopic Hemoclipping in the Treatment of Bleeding Gastric Ulcer. Japanese Abdominal Emergency Medical Society Magazine 1996; 16: 1113-1119.

Zed PJ, Loewen PS, Slavic RS, Marra CA. Meta-analysis of proton pump inhibitors in treatment of bleeding peptic ulcers. Annals of Pharmacotherapy 2001; 35(12): 1528-1534.